Trends in Molecular Medicine

CellPress

Review

Bone–brain crosstalk in osteoarthritis: pathophysiology and interventions

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Osteoarthritis (OA) is a prevalent articular disorder characterized by joint degeneration and persistent pain; it imposes a significant burden on both individuals and society. While OA has traditionally been viewed as a localized peripheral disorder, recent preclinical and clinical studies have revealed the crucial interconnections between the bone and the brain, highlighting the systemic nature of OA. The neuronal pathway, molecular signaling, circadian rhythms, and genetic underpinnings within the bone–brain axis play vital roles in the complex interplay that contributes to OA initiation and progression. This review explores emerging evidence of the crosstalk between the bone and brain in OA progression, and discusses the potential contributions of the bone–brain axis to the development of effective interventions for managing OA.

Highlights

The emerging concept of the 'bone–brain axis' represents a paradigm in our understanding of osteoarthritis (OA), moving from a purely peripheral perspective to recognizing the central role of the brain.

Neuronal pathways are essential for transmitting OA pain signals, directly linking the skeletal system and brain.

Bidirectional communication between bone and brain occurs through molecular signaling. Brain-derived and bone-derived mediators contribute to this communication, and play direct or indirect roles in the development and progression of OA.

Circadian rhythms play a significant role in bone homeostasis and have implications for OA development.

Emerging treatments that target bone–brain crosstalk – such as non-invasive brain stimulation (NIBS), neuropeptides, neurotransmitter drugs, and circadian rhythms regulation – hold promise for improving OA therapeutic outcomes.

Shifting paradigm in understanding OA: the concept of the bone–brain axis

OA is a prevalent articular disorder characterized by multifaceted pathological changes in various joint tissues. The primary symptom of OA is chronic pain, frequently accompanied by impaired mobility and a decline in the quality of life [1]. With a global prevalence exceeding 7%, OA affects more than 500 million individuals [2]. The incidence of OA is expected to rise due to the aging population and increasing rates of obesity [3]. It is anticipated that by the year 2032 nearly 29.5% of individuals aged ≥45 will be diagnosed with OA, emphasizing the urgent need for further research in this area [4]. The symptoms associated with OA, along with the significant healthcare costs involved in managing this chronic condition, impose substantial burdens on individuals, families, and society [5].

Traditionally, OA research has focused mainly on local aspects, often overlooking its broader impacts. However, the pathophysiological mechanisms of OA are highly complex, involving disruptions in homeostasis across multiple systems [6–9]. With a growing emphasis on systemic interactions, recent experimental and clinical research has revealed numerous molecular and physiological mechanisms linking the skeleton and brain. The emerging concept of the 'bone–brain axis' represents a paradigm shift in our understanding of OA, moving from a purely peripheral perspective to recognizing the central role of the brain [10,11]. These two distinct organs communicate bidirectionally during growth and development, and they exhibit a high degree of association at the disease level [12]. Given the reciprocal dependence of the bone and brain, enhancing our understanding of this crosstalk is crucial for comprehending the pathological changes in OA.

In this review, we aim to synthesize the pathophysiology and intervention strategies of OA from a perspective of the bone–brain axis. Specifically, we examine the biological processes underlying the interaction between bone and brain in the occurrence and progression of OA, including the neuronal pathway, molecular signaling, **circadian rhythms** (see Glossary), and genetic factors. Furthermore, we discuss translational efforts by investigating preclinical and clinical research on

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this interactive characteristic within OA. Diverse interventions – such as **non-invasive brain stimulation (NIBS)**, **neuropeptides**, **neurotransmitter** drugs, and circadian rhythms regulation – are considered in this exploration, highlighting their potential therapeutic and preventative implications for OA.

Neuronal pathway in bone–brain crosstalk

The transmission of OA pain signals via sensory nerves represents the most direct and well-studied form of communication between the skeletal system and the brain. Persistent nociceptive stimulation can lead to peripheral sensitization, where sensory neurons in the affected area become increasingly responsive. This process may also trigger central sensitization, amplifying neuronal function and neural signaling within the central nervous system (CNS), consequently intensifying pain perception (Figure 1). These alterations can induce remodeling in both ascending (bottom-up) and descending (top-down) pathways, as well as neural circuits within the spinal cord and brain (Box 1).

In OA, the joint undergoes significant pathological changes marked by local inflammation and tissue damage that stimulate the release of various cytokines and chemokines from both immune

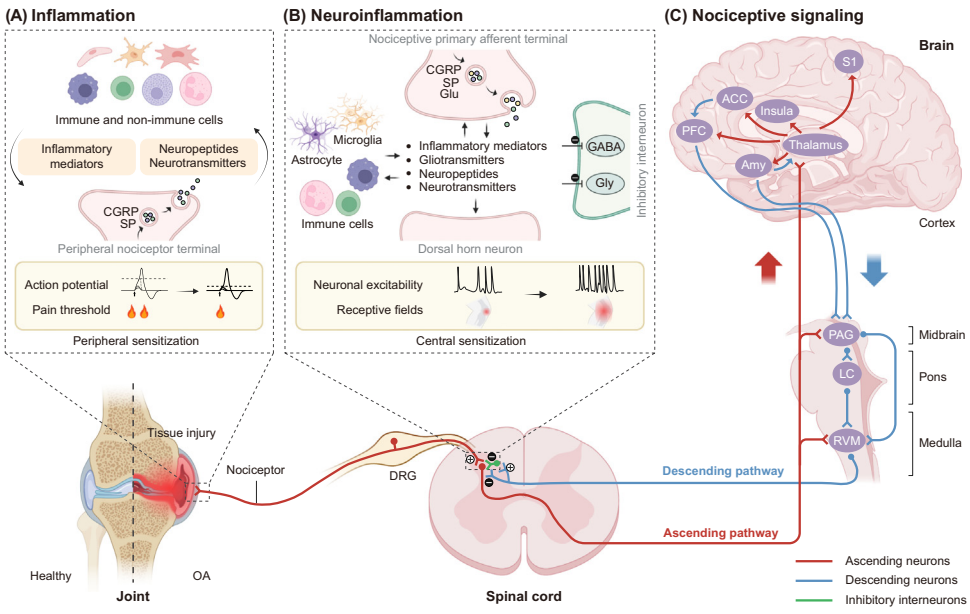

Figure 1. Neural mechanisms of osteoarthritis (OA) pain. (A) OA in the joints initiates an inflammatory cascade and tissue damage, leading to the release of inflammatory mediators from both immune and non-immune cells. These mediators activate nociceptors, generating pain signals. Nociceptors release neuropeptides and neurotransmitters that modulate the function of non-neuronal cells, enhancing peripheral sensitization. (B) Pain signals are transmitted from primary nociceptive neurons to spinal dorsal horn neurons. Concurrently, microglia and astrocytes become activated and proliferate, accompanied by the infiltration of immune cells, leading to the production of proinflammatory cytokines and chemokines. These mediators stimulate spinal dorsal horn neurons, inhibit inhibitory interneurons, and induce central sensitization, which is characterized by increased neuronal excitability and expanded receptive fields. (C) In the ascending pathway, pain signals are transmitted to the thalamus through spinal tracts, generating the experience of pain in the somatosensory cortex (S1) and other brain areas. Meanwhile, the output function of the spinal dorsal horn is regulated by the descending pathway from brain regions such as the brainstem, modulating dorsal horn excitability. Abbreviations: ACC, anterior cingulate cortex; Amy, amygdala; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; GABA, γ-aminobutyric acid; Glu, glutamate; Gly, glycine; LC, locus coeruleus; PAG, periaqueductal gray; PFC, prefrontal cortex; RVM, rostral ventromedial medulla; SP, substance P. Figure created with BioRender.

Box 1. OA-related alterations in the spinal cord and brain

In OA, the continuous nociceptive signaling induces multimodal changes in the spinal cord and brain, resulting in dysregulation of both ascending pain pathways and descending pain modulation systems. Rodent OA models show mechanical hyperalgesia and allodynia, accompanied by a progressive neuroinflammatory response in the spinal dorsal horn and a decrease in **diffuse noxious inhibitory controls (DNICs)** during late-stage OA [110,111]. Individuals with OA also experience hypersensitivity and central hyperexcitability, along with a loss of **conditioned pain modulation (CPM)** [112].

Altered pain-processing brain networks have been observed in rats with monosodium iodoacetate (MIA)-induced OA, characterized by increased activation and enhanced functional connectivity in regions such as the thalamus, hippocampus, and periaqueductal gray (PAG) [113,114]. Human studies have corroborated these findings by revealing abnormalities in brain structure, function, and perfusion in individuals with OA [115–117]. Moreover, patients with OA at different anatomical sites display distinct patterns of gray matter reduction [117]. In addition to partially overlapping with pain processing areas, numerous studies on both OA animal models and OA patients have observed associations between OA pain and cognitive decline, as well as emotional disorders [42,118].

cells (such as macrophages and T cells) and non-immune cells (including **chondrocytes** and synovial fibroblasts) [13,14]. The joint is densely innervated by myelinated and unmyelinated nerve fibers containing abundant nociceptors responsive to mechanical, thermal, and chemical stimuli [15]. These inflammatory mediators activate nociceptors either directly or indirectly, amplifying nociceptive signals. Additionally, they can lower the threshold for action-potential firing in nociceptive neurons via specific receptors, such as transient receptor potential vanilloid 1 (TRPV1), sodium channel Nav1.8, and acid-sensitive ion channels, leading to peripheral sensitization [16]. During peripheral inflammation, nerve growth factor (NGF)–tropomyosin receptor kinase A (TrkA) complexes formed at axonal terminals are transported to the dorsal root ganglion (DRG). This transport triggers the overexpression and release of neuropeptides and neurotransmitters, such as calcitonin gene-related peptide (CGRP) and substance P (SP) [16]. These neuropeptides and neurotransmitters, in addition to modulating the function of non-neuronal cells, are retrogradely transported to the joint, further transmitting nociceptive signals to the spinal cord. Subsequently, the signals ascend to the thalamus and then project to the somatosensory cortex and other brain areas involved in encoding the emotional and cognitive aspects of pain.

The ascending pain pathway is modulated at different levels by endogenous descending control systems originating from various regions of the CNS. Neural structures implicated in descending pain inhibition and/or facilitation include the cerebral cortex, thalamus, and brainstem [17]. Among these structures, the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM) are key components of the descending pain pathway. This pathway can either enhance or inhibit the transmission of pain signals by modulating spinal dorsal horn excitability to varying degrees [18]. In the pathological context of OA, persistent nociceptive signals reach the spinal dorsal horn neurons, leading to reduced activity of inhibitory GABAergic and glycinergic interneurons. This reduction results in diminished inhibition and degeneration of the inhibitory gate control pathway [19,20]. Consequently, there is an overactivity of both ascending and descending facilitatory signals in the pain transmission pathway of the spinal cord, coupled with a deficiency in inhibitory descending signals. This imbalance is a crucial factor contributing to the increased frequency and severity of pain during the OA progression [21,22].

Molecular signaling between bone and brain

The communication between the bone and the brain involves extensive molecular signaling pathways (Figure 2). The brain can send signals downward by releasing **pituitary hormones**, neuropeptides, and neurotransmitters, which can directly regulate bone and join functions [12,23]. Conversely, the skeleton can upwardly regulate brain development and metabolism by producing and releasing various bioactive cytokines [12]. In addition, the immune system, acting as a key intermediary, engages in the interactions between bone and brain. This bidirectional

Glossary

Allodynia: an abnormal pain response to a stimulus that is typically not painful, such as a light touch or mild temperature change.
Blood–brain barrier (BBB): a natural protective membrane formed by tightly connected microvascular endothelial cells in the cerebral capillaries.
Chondrocytes: cells that produce collagen and the extracellular matrix, found in the avascular tissue known as cartilage.
Circadian rhythms: internal biological processes of the 24 h solar day, synchronized with light/dark cycles through light exposure.
Conditioned pain modulation (CPM): the human counterpart of DNIC, with paradigms representing psychophysical protocols used to assess reduced pain sensitivity due to noxious conditioning.
Diffuse noxious inhibitory controls (DNICs): nociceptive inputs modulated by descending inhibition from supraspinal and higher centers.
Extracellular vesicle (EV): a membrane-bound structure containing bioactive molecules, released by cells; EVs are important for mediating the exchange of intercellular biological signals.
Genome-wide association study (GWAS): research aimed at identifying genetic variants associated with specific phenotypes by analyzing differences in allele frequencies between individuals with similar ancestry but differing phenotypes.
Hyperalgesia: an amplifying response to painful stimuli, characterized by increased sensitivity to pain.
Intracortical inhibition: inhibitory activation of interneurons within the cortex, which can be assessed using paired TMS of the motor cortex.
Melatonin: an endogenous hormone, secreted primarily by the pineal gland, that acts on circadian, seasonal, and transgenerational timescales.
Mendelian randomization (MR): a method that uses genetic variants as instrumental variables to assess the causal relationship between a risk factor (exposure) and an outcome.
Neuropeptides: small proteinaceous substances produced and released by neurons that modulate various bodily functions.
Neurotransmitters: endogenous chemicals that allow communication within the nervous system and between

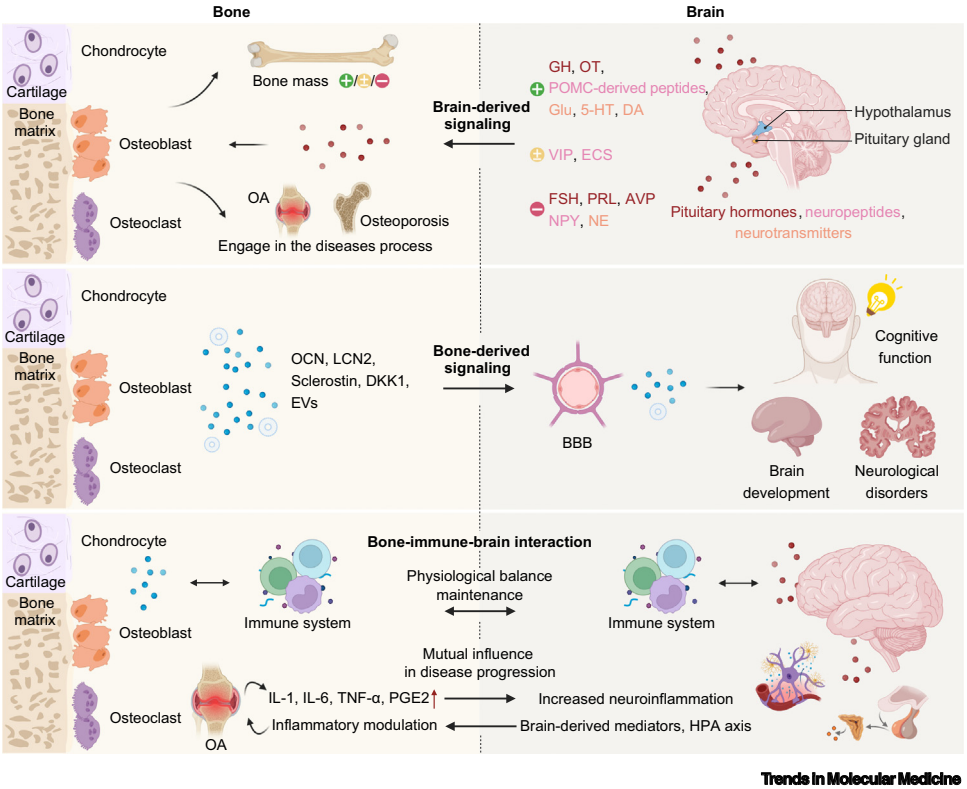

Figure 2. Bidirectional molecular signaling communication between bone and brain. Top: brain-derived signaling, including pituitary hormones, neuropeptides, and neurotransmitters, transmit signals downward to bone, playing a crucial role in regulating bone mass and associated diseases. Middle: several bone-derived signaling mediators also send ascending signals from the periphery to the brain, crossing the blood–brain barrier (BBB) and affecting the central nervous system (CNS), such as cognitive function, brain development, and neurological disorders. Bottom: bidirectional interactions between the bone and brain with the immune system contribute to physiological balance and also exhibit mutual influence in diseases such as osteoarthritis (OA). Abbreviations: AVP, arginine vasopressin hormone; DA, dopamine; DKK1, dickkopf-related protein 1; ECS, endocannabinoid system; EVs, extracellular vesicles; FSH, follicular stimulating hormone; GH, growth hormone; Glu, glutamate; HPA, hypothalamic–pituitary–adrenal; 5-HT, serotonin/5-hydroxytryptamine; IL-1, interleukin 1; IL-6, interleukin 6; LCN2, lipocalin 2; NE, norepinephrine; NPY, neuropeptide Y; OCN, osteocalcin; OT, oxytocin; PGE2, prostaglandin E2; POMC-derived peptides, pro-opiomelanocortin-derived peptides; PRL, prolactin; TNF-α, tumor necrosis factor α; VIP, vasoactive intestinal peptide. Figure created with BioRender.

communication is essential for maintaining homeostasis and plays a significant role in influencing various physiological processes and disease pathogenesis, including OA.

Brain-to-bone communication: brain-derived signaling

Over the past few years, numerous studies have elucidated the role of neuronal signaling in the bone–brain axis. These signaling molecules bind to specific receptors expressed by **osteoblasts** and/or **osteoclasts**, influencing bone formation and regulating bone resorption [11]. In addition to maintaining skeletal homeostasis, some of these neuronal signaling molecules are also crucial in the development of OA (Figure 3).

The hypothalamic–pituitary–skeletal axis is a key pathway associated with the pathology of OA [11,23]. Both preclinical and clinical studies suggest that follicle-stimulating hormone (FSH) may act as a negative regulator in the onset or progression of OA. Specifically, FSH signaling inhibits p38 and activates extracellular signal-regulated protein kinases 1 and 2 (ERK-1/2) phosphorylation, leading to decreased collagen type II α-1 (*Col2a1*) synthesis. This process affects

neurons and their target tissues during synaptic transmission.

Non-invasive brain stimulation (NIBS): a technique that modulates specific brain regions safely and non-invasively, adjusting neuronal activity to improve or alter the function of targeted areas.

Osteoblasts: bone-forming cells that synthesize bone matrix and coordinate the mineralization of the skeleton.

Osteoclasts: bone-resorbing cells that resorb old or damaged bone and digest the protein matrix.

Pituitary hormones: chemical messengers produced by the pituitary gland that play a vital role in regulating the functions of other endocrine glands.

RNA sequencing (RNA-seq): a high-throughput sequencing technology that converts mRNA into complementary DNA for sequencing, providing comprehensive insights into gene expression and enabling the discovery of novel transcripts.

Suprachiasmatic nucleus (SCN): the principal circadian pacemaker in mammals, located in the hypothalamus, which coordinates subordinate cellular clocks throughout the body.

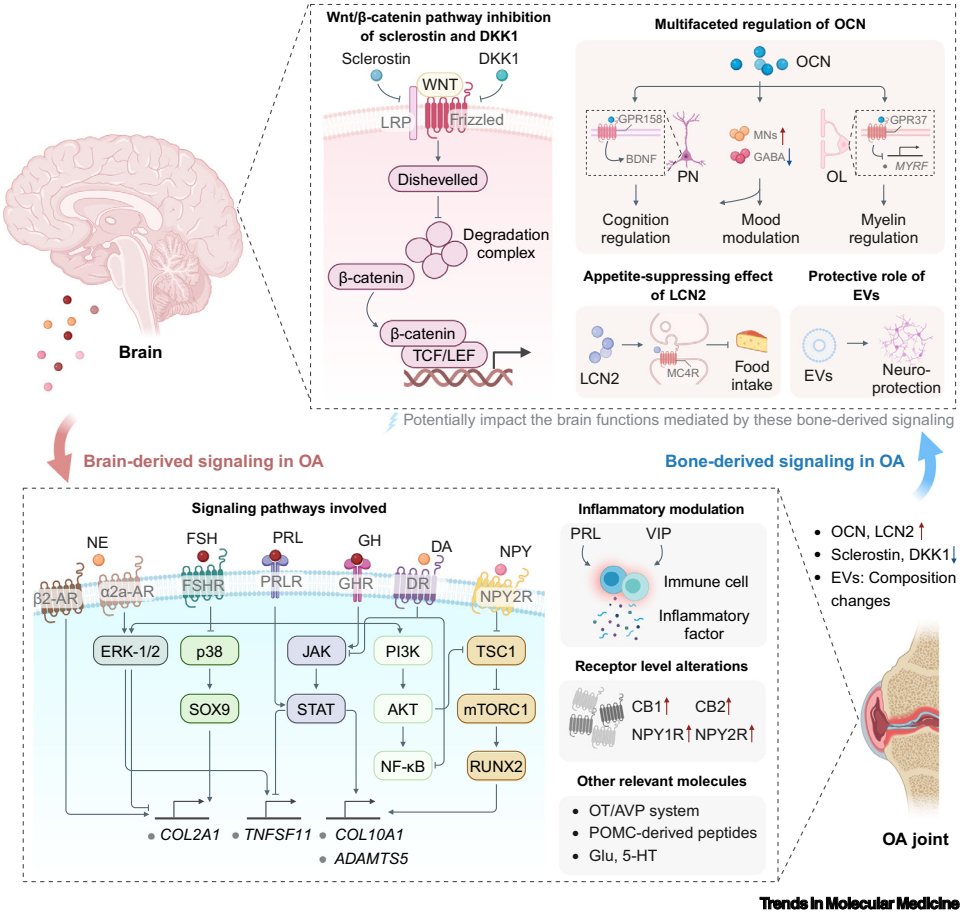

Figure 3. Brain- and bone-derived molecular signaling in osteoarthritis (OA) progression. Brain-derived signaling molecules play a crucial role in OA pathogenesis by regulating key OA-related pathways through their receptors. They also modulate joint inflammation, exhibit receptor-level alterations, and are associated with disease progression and related symptoms. Conversely, signaling molecules derived from bone are dysregulated in OA, and could influence brain function through different pathways and receptors. Abbreviations: *ADAMTS5*, a disintegrin and metalloproteinase with thrombospondin motifs 5; AKT, protein kinase B; AR, adrenoceptor; AVP, arginine vasopressin hormone; BDNF, brain-derived neurotrophic factor; CB, cannabinoid receptor; *COL2A1*, collagen type II alpha-1; *COL10A1*, collagen type X alpha 1 chain; DA, dopamine; DKK1, dickkopf-related protein 1; DR, DA receptor; ERK-1/2, extracellular signal-regulated protein kinases 1 and 2; EVs, extracellular vesicles; FSH, follicular stimulating hormone; FSHR, FSH receptor; GABA, γ-aminobutyric acid; GH, growth hormone; GHR, GH receptor; Glu, glutamate; GPR, G protein-coupled receptor; 5-HT, serotonin/5-hydroxytryptamine; JAK, Janus kinase; LCN2, lipocalin 2; LRP, low-density lipoprotein receptor protein; MC4R, melanocortin 4 receptor; MNs, monoamine neurotransmitters; mTORC1, mechanistic target of rapamycin complex 1; *MYRF*, myelin regulatory factor; NE, norepinephrine; NF-κB, nuclear factor kappa B; NPY, neuropeptide Y; NPY1R, NPY1 receptor; NPY2R, NPY2 receptor; OCN, osteocalcin; OL, oligodendrocyte; OT, oxytocin; PI3K, phosphoinositide 3-kinase; PN, pyramidal neurons; POMC-derived peptides, pro-opiomelanocortin-derived peptides; PRL, prolactin; PRLR, PRL receptor; RUNX2, Runt-related transcription factor 2; SOX9, SRY-box transcription factor 9; STAT, signal transducer and activator of transcription; TCF/LEF, T cell factor/lymphoid enhancer binding factor; *TNFSF11*, necrosis factor superfamily member 11; TSC1, tuberous sclerosis 1; VIP, vasoactive intestinal peptide. Figure created with BioRender.

chondrocyte dedifferentiation and cartilage destruction, potentially promoting OA development [24]. Moreover, elevated serum FSH levels in postmenopausal women with knee OA (KOA) are linked to more severe cartilage damage, which may be mediated through the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/nuclear factor κB (NF-κB) pathways [25]. By contrast,

prolactin (PRL) exhibits a protective effect against joint inflammation by inhibiting the expression of receptor activator of NF-κB ligand (RANKL) encoded by tumor necrosis factor superfamily member 11 (*Tnfsf11*) through a signal transducer and activator of transcription-3 (STAT3)-dependent pathway in rodent arthritis models. It reduces joint swelling, mitigates inflammation, and decreases osteoclast density [26]. Studies suggest a potential inverted U-shaped relationship between OA and growth hormone (GH)/insulin-like growth factor-1 (IGF-1) signaling, with both excessively high and low levels of GH/IGF-1 being associated with joint diseases [27]. Chronic GH/IGF-1 deficiency in dwarf rodents correlates with more severe OA joint cartilage lesions [28]. Excessive GH, however, triggers chondrocyte metabolic dysfunction through the Janus kinase (JAK)/STAT5 signaling cascade, characterized by increased expression of the chondrocyte hypertrophy markers collagen type X α1 chain (*Col10a1*) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (*Adamts5*), leading to OA development [29]. Moreover, activation of the oxytocin (OT)/arginine vasopressin (AVP) system has been observed in monosodium iodoacetate (MIA)-induced rat OA models, potentially modulating the pain pathway [30].

The brain communicates with bone through various neuropeptides released from the hypothalamus, which are implicated in the occurrence and development of OA [11]. A study in rodent OA models has shown that neuropeptide Y (NPY) promotes the progression of OA, as indicated by cartilage degradation and the upregulation of *Col10a1*, *Adamts5*, and matrix metallopeptidase 13 (*Mmp13*). This effect primarily occurs through the activation of the mechanistic target of rapamycin complex 1 (mTORC1) pathway in an NPY2 receptor (NPY2R)-dependent manner, as evidenced by changes in the levels of its upstream and downstream factors. In human OA cartilage, NPY is overexpressed, accompanied by increased expression of the NPY1 receptor (NPY1R) and NPY2R [31]. Although the precise role of vasoactive intestinal peptide (VIP) in OA pathogenesis remains unclear, changes in VIP concentrations in synovial fluid (SF) in OA have been associated with increased production of proinflammatory cytokines, potentially leading to pain, joint inflammation, and cartilage degeneration [32]. Additionally, joint inflammation disrupts the spinal and intra-articular endocannabinoid system (ECS), characterized by alterations in anandamide synthesis and degradation enzymes, along with upregulation of synovial cannabinoid receptors (CBs) [33,34]. Pro-opiomelanocortin (POMC)-derived peptides, which are multifunctional precursors for various peptide hormones – such as adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormones (MSH), and β-endorphin – have been detected in the joints of OA patients [35]. In KOA patients, the concentration of synovial α-MSH is negatively correlated with disease severity and inflammatory levels, while circulating levels of β-endorphin at rest show a positive correlation with mechanical pain sensitivity [36,37].

In the central regulation of bone, neurotransmitters are also involved in both normal physiological processes and bone disease progression. For instance, patients with OA and joint injuries exhibit increased concentrations of the excitatory neurotransmitter glutamate (Glu) in SF, which acts on nerves to induce pain and promote inflammation and degeneration in joint tissues [38,39]. Norepinephrine (NE), the primary neurotransmitter of the sympathetic nervous system, exerts multiple effects through different receptors in the pathogenesis of OA. Both α_2- and β_2-adrenoceptors (ARs) are majorly involved in the OA process, with α_2-ARs upregulating RANKL and downregulating collagen type II via the ERK-1/2 pathway, while β_2-ARs upregulate collagen type II [40,41]. Furthermore, serotonin (5-hydroxytryptamine, 5-HT) serves as a mediator in promoting peripheral pain sensitization and is associated with neurochemical changes underlying pain in OA [42,43]. Additionally, experimental studies suggest that dopamine (DA) exerts chondroprotective effects, possibly by inhibiting the NF-κB and JAK2/STAT3 signaling pathways in OA, while an abnormal expression pattern related to DA has also been identified in OA patients [44,45].

Bone-to-brain communication: bone-derived signaling

Beyond its classical roles, the skeleton functions as an endocrine organ with significant involvement in various physiological processes. Some bone-derived regulators enter the bloodstream through the close connection between bone cells and blood vessels, sending 'upward' signals that impact the brain, with the potential to traverse the **blood–brain barrier (BBB)**. These regulators can directly influence brain development and cognitive function, and may be associated with neurological diseases [10].

Several bone-derived signaling molecules that influence brain function are dysregulated in OA (Figure 3). For example, osteocalcin (OCN), secreted solely by osteoblasts and serving as a biomarker for bone health, shows elevated serum levels with increasing OA severity [46]. OCN also plays a crucial role in cognitive development, mood modulation, and myelin homeostasis, which may be mediated by brain-derived neurotrophic factor (BDNF) expression through G protein-coupled receptor 158 (GPR158) in pyramidal neurons, increased monoamine neurotransmitters (MNs) with reduced γ-aminobutyric acid (GABA) levels, and myelin regulatory factor (*Myrf*) inhibition via GPR37 in oligodendrocytes (OL) [47,48]. Additionally, lipocalin 2 (LCN2) protein levels are upregulated in OA patients and OA mouse models [49]. Bone-derived LCN2 suppresses appetite by binding to the melanocortin 4 receptor (MC4R) in hypothalamic neurons [50]. The Wnt/β-catenin signaling pathway is a well-established regulator of cartilage homeostasis and OA pathophysiology. Its endogenous inhibitors, sclerostin and dickkopf-related protein 1 (DKK1), highly expressed in bone, are reduced in the SF and serum of OA patients [51,52]. A recent study has revealed that osteocyte-derived sclerostin impairs synaptic plasticity and memory by dysregulating Wnt/β-catenin signaling in aged mice [53]. Furthermore, circulating levels of DKK1 and sclerostin are negatively associated with cognitive function, suggesting their potential as predictive markers and therapeutic targets for neurodegenerative diseases [53,54]. In addition to these osteokines, the composition of **extracellular vesicles (EVs)** released by joint tissues is altered during OA [55]. EVs from bone cells act as key messengers in signal exchange within the bone–brain axis and have the potential to preserve brain function [56].

Considering the crucial role of these bone-derived regulators in modulating brain functions, it is plausible that their abnormal expression patterns in OA could potentially affect the brain, increasing susceptibility to brain disorders. Nonetheless, studies investigating the specific bone-to-brain signaling mechanisms of these molecules in the context of OA are still limited, and these mechanisms require in-depth investigation.

Bidirectional communication: immune-mediated signaling

The bone and brain engage in bidirectional interactions with the immune system, sharing a variety of molecules such as chemokines, cytokines, and transcription factors. These interactions involve reciprocal regulation between the bone and brain with immune cells, collectively contributing to the maintenance of overall homeostasis [57,58]. Furthermore, tissue-resident macrophages in the bone and brain (osteoclasts and microglia, respectively) exhibit common molecular pathways crucial for both physiological and pathological processes [59].

In the context of OA, alongside dysregulated local inflammation driven by risk signals, low-grade systemic inflammation is linked to disease progression. Circulating levels of various proinflammatory mediators – including interleukin 1 (IL-1), IL-6, tumor necrosis factor α (TNF-α), and prostaglandin E2 (PGE2) – are significantly elevated in OA [60]. These persistent inflammatory states, originating from peripheral joints, may increase BBB permeability, thereby affecting brain health. For example, in mouse models, the induction of OA increases neuroinflammation in the brain, as indicated by the upregulation of mRNAs for inflammatory cytokines IL-1β and TNF-α,

subsequently accelerating β-amyloid (Aβ) deposition and neuronal loss [61]. Increased neuroinflammation has also been observed in OA patients, such as elevated levels of inflammatory proteins in cerebrospinal fluid (CSF) correlating with serum levels, and increased Aβ-related tau deposition in patients combined with Aβ-positivity [6,62].

Conversely, several brain-derived molecules (e.g., PRL and VIP) regulate systemic and joint levels of inflammatory mediators through interactions with immune cells in OA [26,32]. Activation of the hypothalamic–pituitary–adrenal (HPA) axis promotes the release of the anti-inflammatory hormone cortisol [30,63]. Additionally, a recent study suggests that peripheral inflammation (non-OA-specific) activates the central nucleus of the solitary tract, enabling direct neural control of immune responses, potentially offering further insights into neuro–immune–skeletal interactions in OA pathology [64].

Circadian rhythms in bone–brain crosstalk

Throughout the body, the central pacemaker **suprachiasmatic nucleus (SCN)** conveys temporal information to secondary, self-sustained circadian clocks in peripheral tissues via various timing cues, such as humoral and neural signals, body temperature rhythms, and rest–activity patterns. This synchronization of circadian rhythms regulates numerous physiological and behavioral processes, serving as a bridge in the bone–brain connection [65,66] (Figure 4). Bone tissue also exhibits circadian gene expression, particularly of the core transcriptional activator brain and muscle Arnt-like 1 (*BMAL1*), which is essential for circadian pace-making and the regulation of bone resorption and formation [67]. The advent of **RNA sequencing (RNA-seq)** technology has opened new avenues to investigate potential associations between disruptions in circadian

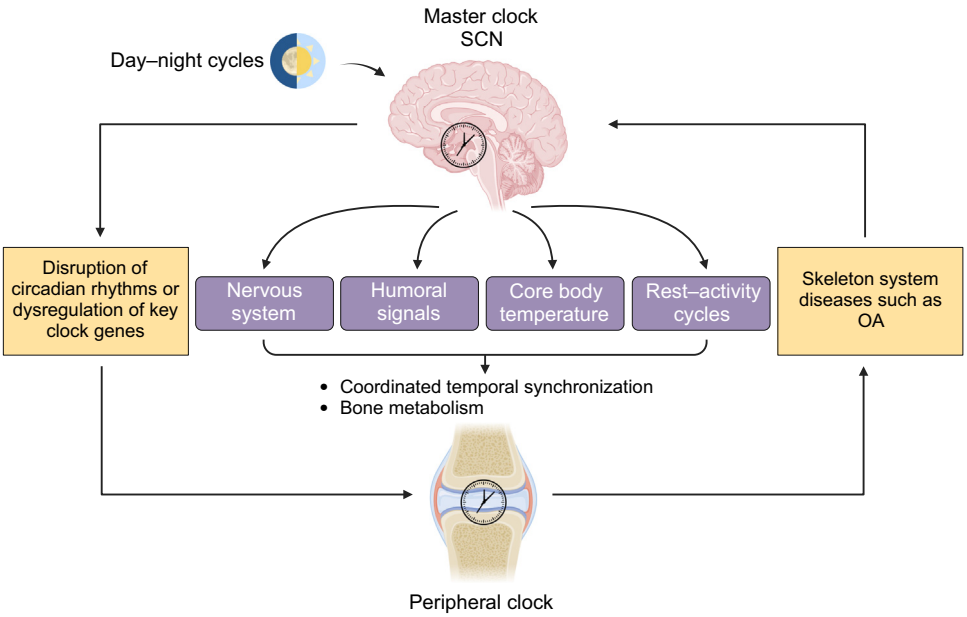

Figure 4. Circadian rhythms in the bone–brain axis. Day–night cycles entrain the master clock in the suprachiasmatic nucleus (SCN). The SCN then transmits temporal information to peripheral circadian clocks in bone via timing cues such as neural and humoral signals, body temperature rhythms, as well as rest–activity cycles, coordinating temporal synchronization and regulating bone metabolism. Disruptions in circadian rhythms or dysregulation of key clock genes can result in a range of pathologies, increasing the risk of skeleton system diseases such as osteoarthritis (OA). These diseases may also disrupt circadian rhythms and adversely affect overall health. Figure created with BioRender.

rhythms and the progression of OA across different species, enabling the analysis of gene expression changes across various time points.

The bidirectional influence between disrupted circadian rhythms and OA has been consistently observed across different species [68]. Abnormal circadian rhythm patterns have been observed in both OA model animals and OA patients. For instance, levels of key clock genes, such as the transcription inhibitor cryptochrome 2 (*CRY2*) and *BMAL1*, were markedly reduced in OA cartilage tissue [69–71]. Additionally, the population of BMAL1-positive chondrocytes exhibited a progressively decrease with increasing disease severity [69]. RNA-seq analysis of cartilage from OA patients has further revealed that circadian rhythm pathways are among the most significantly dysregulated [72]. Conversely, disturbances in the light–dark (LD) cycle disrupt circadian rhythms in mice, leading to reduced rhythmicity in the central circadian pacemaker. This disruption subsequently triggers inflammation and metabolic disturbances in bone, resulting in pathological changes that resemble OA [73,74]. Moreover, results from time-series RNA-seq have demonstrated that disruption of chondrocyte *Bmal1* abolishes rhythmicity, leading to dysregulated transforming growth factor β (TGF-β) and nuclear factor of activated T cells (NFAT) signaling, as well as reduced expression of key matrix-related genes, including SRY-box transcription factor 9 (*Sox9*), aggrecan (*Acan*), and *Col2a1*. This disruption in inflammatory and catabolic pathways, along with decreased anabolic signaling, contributes to OA-like progressive degeneration of articular cartilage [69].

Genetic underpinnings of bone–brain crosstalk

With the rapid advancement of modern genome sequencing technologies and the availability of biobank-scale phenotypic and genetic data, increasing evidence has elucidated the genetic connections within the bone–brain axis. For example, a recent **genome-wide association study (GWAS)** identified overlapping genetic variants between human intracranial volume and bone mineral density (BMD) [75]. Additionally, various brain imaging-derived phenotypes (BIDPs) have shown genetic correlations with BMD across different anatomical regions. **Mendelian randomization (MR)** analysis has further revealed a causal relationship between BIDPs and BMD, with notable causal associations observed in several left brain regions [76].

At the disease level, multiple genetic loci associated with OA are predicted to contain expression quantitative trait loci (eQTLs) in the frontal cortex and/or amygdala, suggesting potential links between OA pathogenesis and gene expression alterations in these brain tissues [77]. A meta-analysis of GWAS across multiple cohorts has also revealed that a subset of high-confidence OA effector genes is associated with neuronal function and development [9]. Furthermore, the solute carrier family 39 member 8 (*SLC39A8*) gene, which encodes a transmembrane transporter responsible for mediating the cellular uptake of various metal ions, shows pleiotropy between KOA and accelerated brain aging. Its spatial expression pattern across the brain has been associated with the brain aging patterns in KOA. This gene is implicated in both the inflammatory progression of OA and the regulation of synaptic plasticity and cognitive function in the brain, shedding light on the genetic basis underlying cognitive decline in KOA patients [78]. Furthermore, a close genetic correlation exists between OA and major depressive disorder (MDD), with shared causal variants indicating a mutual risk conferred by genetic liability to these two diseases [79].

Intervention approaches targeting bone–brain axis for OA

Current interventions for OA primarily aim to alleviate pain and improve joint function (see Clinician's corner). However, these methods often carry associated adverse events and health risks, which may fail to fully meet the diverse needs of all patients [80]. In recent years, the growing understanding of the pathophysiology of OA within the bone–brain axis leads to the development of potential therapeutic approaches. These strategies include NIBS therapy, neuropeptides,

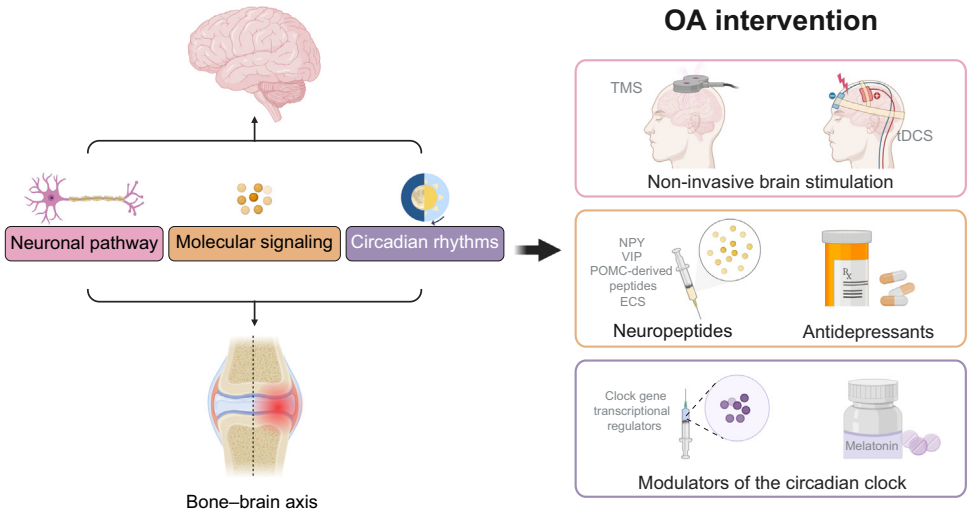

Figure 5. Managing osteoarthritis (OA) via the bone–brain axis. The bidirectional communication between the bone and brain involves several pathways, including the neuronal pathway, molecular signaling, and circadian rhythms. Given the characteristics of the bone–brain axis, multimodal and multidisciplinary approaches should be used for the effective treatment of OA patients. Abbreviations: ECS, endocannabinoid system; NPY, neuropeptide Y; POMC-derived peptides, pro-opiomelanocortin-derived peptides; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; VIP, vasoactive intestinal peptide. Figure created with BioRender.

neurotransmitter medications, and circadian rhythms regulation (Figure 5). Combining these advancements with traditional treatments can enhance therapeutic efficacy, offering a more comprehensive and integrated approach for managing OA.

Brain stimulation approaches modulating cortical excitability

NIBS encompasses various techniques, each with distinct neural mechanisms in alleviating OA pain [81]. In the following section we summarize two major modalities: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

By generating a magnetic field via an electromagnetic coil placed on the scalp, TMS induces electrical currents in specific regions of the cerebral cortex, typically targeting the motor cortex. This technique can either activate or inhibit neuronal activity, thus serving the dual role of measuring and modulating brain function [82]. In patients with KOA, significant associations were observed between increased **intracortical inhibition**, as measured by TMS, and lower pain. These findings suggest that motor cortex inhibition is a potential marker of adaptation to chronic pain in KOA [83]. Additionally, one session per month of repetitive TMS (rTMS) at 10 Hz over the motor cortex contralateral to the affected OA joint improved pain and psychological symptoms associated with central sensitization in KOA patients [84].

tDCS can reduce OA pain by enhancing cortical excitability. Its primary mode of action involves applying a low-intensity constant electrical current to the head via anode and cathode electrodes, modulating neuronal membrane potentials in a polarity-specific manner [85]. In a rat model of MIA-induced OA, tDCS has demonstrated significant therapeutic effects by reversing mechanical hypersensitivity and thermal **hyperalgesia**. These effects are associated with an increase in N-methyl-D-aspartate (NMDA) receptor expression in the PAG and a suppression of BDNF/tropomyosin-related kinase B (TrkB) signaling in the descending pain modulation system [86,87]. Clinical observations in OA patients – with the anode of tDCS placed over the primary

motor cortex of the hemisphere contralateral to the painful area, and the cathode over the supraorbital area on the ipsilateral side – have demonstrated significant pain relief without apparent adverse reactions or cognitive changes [88]. These positive outcomes are likely associated with a reduction in both the quantity and intensity of pain-related functional brain connections [89].

Pharmacological approaches regulating molecular signaling

The regulatory role of neuropeptides within the bone–brain axis highlights their potential for treating inflammatory and degenerative joint diseases [35]. For instance, NPY2R antagonists significantly alleviate the severe OA pathology induced by NPY, effectively mitigating chondrocyte hypertrophy and cartilage matrix degradation [31]. Furthermore, both *in vivo* and *in vitro* experiments suggest the VIP may treat OA by regulating chondrocyte apoptosis, promoting extracellular matrix (ECM) deposition, suppressing the NF-κB inflammatory signaling pathway, and reducing inflammatory cytokine levels in OA chondrocyte and animal models [90]. Similarly, POMC-derived peptides, such as α-MSH, exhibit promising anti-inflammatory and cartilage-protective activities in OA interventions by modulating inflammatory cytokines and ECM dynamics in human chondrocytes with an inflammatory phenotype [91]. These preclinical findings suggest that drugs targeting these neuropeptides and their receptors hold promise as potential therapeutic options for OA.

Preclinical evidence supports the significant role of the ECS in reducing inflammation, alleviating pain, and providing neuroprotection in OA [92–94]. For instance, one study proposed that targeting cannabinoid receptor type 1 (CB1)-dependent fatty-acid amide hydrolase (FAAH) inhibition could reduce pain hypersensitivity and mechanical **allodynia** in rats with MIA-induced OA. This treatment also improved memory recognition, reduced depressive-like behavior, restored long-term potentiation, and normalized monoamine levels in the hippocampus [42]. However, despite promising preclinical findings, the clinical translation of medical cannabis for OA patients has been limited, yielding less satisfactory results [95]. Additionally, the safety profile and side effects of medical cannabis require further evaluation and comparison with other medications.

Given the mechanisms of central sensitization in OA and the crucial role of neurotransmitters in the bone–brain crosstalk, targeting specific neurotransmitters has emerged as a promising strategy for managing OA. Recent studies have highlighted the effectiveness of antidepressant medications in modulating inhibitory signals associated with pain reduction, showing their potential in managing OA. In rodent models, serotonin–norepinephrine reuptake inhibitors (SNRIs) have demonstrated reductions in tactile allodynia and resting pain [96]. Furthermore, vortioxetine, a novel antidepressant drug that acts as a serotonin reuptake inhibitor, has dose-dependently reduced cold allodynia, reversed cognitive impairment, and had no adverse effects on well-being or cardiac redox status in rats with MIA-induced OA [97]. Nonetheless, randomized controlled trials (RCTs) have yielded mixed results regarding the efficacy of antidepressants, and their use is linked to an increased risk of adverse effects, such as constipation, nausea, cough, palpitations, and decreased appetite [98–100]. Therefore, careful patient selection is essential to optimize clinical benefits while weighing the risks and benefits of these medications.

Additional approaches through circadian rhythm mechanisms

The disruption of circadian rhythm in OA presents possibilities for developing interventions aimed at correcting abnormal circadian rhythm expression patterns. Studies using OA mouse models and IL-1β-induced cartilage explant degeneration have demonstrated that agonists and/or antagonists targeting retinoid-related orphan receptors (RORs) and REV-ERB, which regulate *BMAL1* transcription, significantly restore OA-related circadian rhythm disruptions and alleviate pathological conditions. This intervention resulted in reduced mechanical allodynia and cartilage

Clinician's corner

OA is a multifaceted bone disease marked by cartilage degradation, synovial inflammation, and subchondral bone remodeling. As the disease progresses, these pathological changes lead to joint stiffness, pain, and loss of mobility. This progression not only impairs joint function but also contributes to broader systemic effects, significantly impacting brain health and quality of life.

Current intervention strategies for OA focus primarily on symptomatic relief, including pharmacological approaches (such as nonsteroidal anti-inflammatory drugs, opioids, and corticosteroids), non-pharmacological interventions (e.g., weight management and massage), and surgical procedures (including arthroscopic examination and joint replacement). However, these strategies often prove unsatisfactory and are frequently associated with substantial adverse effects, highlighting the need for improved therapeutic approaches.

The neuronal pathway, molecular signaling, circadian rhythms, and genetic underpinnings of the bone–brain axis are all involved in the pathological processes of OA. An in-depth understanding of the interactive characteristics of the bone–brain axis can help identify modifiable targets, refine existing treatment protocols, and develop more systematic preventive measures.

Emerging therapies targeting the bone–brain axis show promise in alleviating pain, mitigating inflammation, reducing cartilage degradation, and protecting brain function. However, further animal studies and RCTs are necessary to establish a more comprehensive understanding of their safety and efficacy, as well as to determine the most appropriate treatment approaches for each stage of the disease.

Establishing early biomarkers of OA is essential for effective disease management. The complex interactions within the bone–brain axis not only reflect local pathological changes in the joints but may also reveal systemic and neurological alterations. These biomarkers can facilitate early diagnosis and timely

degeneration, as evidenced by increased collagen synthesis, reduced catabolism, and decreased collagen denaturation [101,102]. These findings suggest that targeting regulators of clock genes could be a potential approach for implementing chronotherapy in OA.

Melatonin has emerged as a promising therapeutic approach for OA. Research in rats with collagenase-induced OA has shown that melatonin can restore the expression of clock-controlled genes, thereby rectifying the abnormal phenotype of chondrocytes. When combined with exercise, melatonin more effectively prevents periarticular muscle damage and cartilage degeneration [103]. Its efficacy in alleviating OA is linked to the direct or indirect regulation of key circadian clock genes, including transcriptional activators (e.g., *BMAL1*), transcriptional repressors (e.g., *CRY2*), and nuclear hormone receptors (e.g., *RORs* and *REV-ERB*), thus maintaining cartilage matrix homeostasis [104]. Additionally, melatonin exhibits anti-inflammatory and antioxidant effects, enhancing its potential in preventing and treating OA [105–107].

Concluding remarks

OA is not solely a local peripheral disease but rather a systemic disorder involving the interplay between the bone and brain. Approaching OA from the perspective of bone–brain crosstalk allows for better understanding of the underlying mechanisms and potential therapeutic targets. This viewpoint opens up possibilities for managing OA through multimodal and multidisciplinary interventions that target various systems, aiming to alleviate both physiological and psychological discomfort in patients.

Despite extensive research, controversies and gaps remain in our understandings of the mechanisms and clinical translation of OA. One major challenge lies in the limitations of existing animal models, which struggle to fully replicate the pathophysiological mechanisms of human OA [108]. Differences in disease complexity and species anatomy contribute to these limitations, resulting in insufficient mechanistic research and discrepancies between findings from experimental animal models and clinical studies. Moreover, previous RCTs have faced issues such as inappropriate blinding, lack of a reliable placebo control, inadequate interventions, small sample sizes, and short follow-up periods, leading to inconsistent outcomes and a lack of consensus. Additionally, our understanding of the genetic and molecular mechanisms underlying OA, particularly the bidirectional communication between bone and brain, remains incomplete. The molecular mechanisms and precise efficacy of emerging interventions targeting the bone–brain axis mechanisms are also not yet fully understood.

The exploration of the bone–brain axis in OA remains largely underexplored, underscoring the need for further research to elucidate its role in OA development and progression (see Outstanding questions). Future studies should focus on elucidating the causal relationships and molecular mechanisms of bone–brain interactions across various disease stages, aiming to identify targets for clinical applications. A recent study leveraged multimodal patient data, including clinical biomarkers, genomics, metabolomics, and proteomics, to develop a machine-learning model capable of pinpointing risk biomarkers and predicting individual risk up to 5 years before a diagnosis of OA [109]. These advances in multiomics technologies (e.g., RNA-seq, whole-genome sequencing, mass spectrometry) and the integration of interpretable machine-learning models offer promising opportunities for identifying biomarkers related to the bone–brain axis, which could enhance early diagnosis and preventive strategies. Additionally, personalized and precision treatments should be further refined to address the unique needs of individual patients based on their specific bone–brain interaction profiles, while also minimizing side effects. It is crucial to underscore the substantial evidence linking OA with brain diseases, suggesting that protecting against OA also contributes to preserving brain health. Given the

prevention, ultimately improving patient outcomes.

By identifying individual risk factors for the disease, personalized prevention strategies should be developed that consider modifiable risk factors and individual differences. Additionally, given the close interaction between the bone and brain, enhancing the protection of brain function is particularly important.

importance of bone–brain crosstalk, a more comprehensive approach to understanding and managing OA – and other skeletal conditions such as osteoporosis and fractures – is essential for promoting overall health and well-being.

Author contributions

Y.L.T. and Y.H.T. wrote the manuscript and prepared the figures. W.Z.Y., J.C., and Y.H.T. edited the manuscript. All authors contributed to the final version of the manuscript.

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Declaration of interests

The authors declare no competing interests.

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Outstanding questions

How can we develop more accurate animal models that better replicate the diverse etiologies and stages of human OA, thereby enhancing the translatability of research findings to clinical scenarios?

What are the specific brain abnormalities associated with OA, and how do they contribute to the progression of the disease beyond the scope of local inflammation?

Does the dysregulation of bone-derived signals in the pathological state of OA affect the functional modulation of the brain mediated by these signals?

Are there specific neuro–immune–skeletal interaction patterns in OA beyond those induced by OA-related pain, and what are the underlying mechanisms driving these interactions?

What are the overlapping molecular pathways and genetic mechanisms between bone and brain in the context of OA, and how do they influence disease development and progression?

How can insights into the bone–brain axis inform the development of novel therapeutic approaches and sensitive early diagnostic biomarkers for OA?

How can we establish a framework for RCTs that enables more precise and effective management strategies for OA?

How can we break the vicious cycle linking bone and brain diseases to promote overall body homeostasis and health?

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