

Review

Reevaluating thalamic contributions to pain: A translational framework for precision neuromodulation

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ARTICLE INFO

Keywords:

Thalamus

Chronic pain

Cross-species

Neuromodulation

Precision neuromodulation framework

ABSTRACT

The thalamus plays a central role in processing both acute and chronic pain. Yet, identifying specific thalamic targets and effective strategies for pain management remains a pivotal challenge. By integrating cross-species evidence, this review synthesizes both a functional re-examination of thalamic nuclei in pain and a critical evaluation of targeted neuromodulation strategies, aiming to guide the advancement of precision pain medicine. We emphasize that the sensory and affective dimensions of pain are functionally intertwined and context-dependent, supporting a re-evaluation of thalamic pain pathways as integrated components of cortico-limbic networks rather than segregated sensory or affective relays. Specifically, while ventral and posterior thalamic nuclei (VPTN) contribute not only to sensory discrimination but also to hypersensitivity states, medial and intralaminar nuclei (MITN) integrate sensory-affective signals and facilitate pain-related emotional comorbidities. Our systematic evaluation highlighted several key translational challenges: poorly delineated anatomical boundaries and overlapping microcircuits within thalamic nuclei, undefined stimulation parameter spaces, translational barriers from species differences, and the complex interplay between neuroplasticity and individual differences in pain networks. To address these challenges, we propose a precision neuromodulation framework incorporating high-resolution targeting, multidimensional parameter optimization, cross-species validation, alongside artificial intelligence (AI)-driven adaptive closed-loop systems. This integrated approach may advance chronic pain therapy from generalized symptom control toward mechanism-based and personalized pain therapies.

1. Introduction

Chronic pain affects an estimated 20–40% of adults worldwide, creating substantial disability and economic costs [1,2]. In 2020, low back pain alone impacted approximately 619 million individuals globally, with projections anticipating a rise to 843 million cases by 2050. This increase is projected to result in 832 years lived with disability (YLDs) per 100,000 population [3]. Current pharmacological treatments are often inadequate, largely due to the risks of opioid dependency and adverse effects associated with nonsteroidal anti-inflammatory drugs (NSAIDs) [4–6]. While neuromodulation holds promise as a non-pharmacological intervention,

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<https://doi.org/10.1016/j.plrev.2026.02.001>

Received 14 November 2025; Received in revised form 18 January 2026; Accepted 6 February 2026

Available online 7 February 2026

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especially deep brain stimulation (DBS), its clinical effectiveness remains insufficiently validated [7]. This persistent gap in treatment underscores the urgent need to reexamine central pain mechanisms, with a particular focus on the thalamus, a pivotal brain region for integrating all sensory information underpinning conscious perception. Its functionally specialized nuclei process all sensory modalities, including chemosensation, despite the common view that olfaction and taste are less reliant on thalamic relay [8,9]. Serving as the central hub for nociceptive signaling, the thalamus transforms peripheral inputs into conscious pain perception while simultaneously coordinating threat responses, reflecting an evolutionarily conserved function. The clinical importance of thalamic involvement in pain processing became increasingly apparent in the early 20th century, when neurologists documented severe neuropathic pain syndromes following lesions in the lateral thalamus [10,11]. These pioneering observations highlighted the thalamus's dual role as both a pain transmitter and modulator, establishing that dysfunction within this structure alone could lead to the development of chronic pain.

Modern pain neuroscience conceptualizes pain as a complex, multidimensional experience that encompasses sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions [12]. This perspective originally gave rise to a functional division within the thalamus [13]: (1) the lateral pathway, including projections from the ventral posterolateral nucleus (VPL) to the primary and secondary somatosensory cortices (S1 and S2), which primarily processes aspects such as pain location, intensity, and temporal patterns [14,15]; (2) the medial pathway, connecting medial thalamic nuclei like the mediodorsal nucleus (MD) with the anterior cingulate cortex (ACC), is thought to govern the affective salience and behavioral responses [16,17]. Nonetheless, recent findings suggest a more integrated view, in which the sensory and affective dimensions of pain are tightly intertwined and potentially covary across contexts, thereby supporting a re-evaluation of thalamic pain pathways as components of cortico-limbic networks rather than isolated sensory or affective relays. This is illustrated by the medial and intralaminar thalamic nuclei (MITN), particularly the MD and paraventricular nucleus (PVT), which appear to support integrated processing of sensory and affective signals through cortico-limbic networks [18–22]. A growing body of circuit-level evidence substantiates this view. For example, Meda and colleagues demonstrated that the projection from the MD to the ACC amplifies pain-related negative affect in animal models [18]. Complementing this finding, You et al. have shown that pharmacological inhibition or lesions of the MD can reduce hyperalgesia in rats exposed to hypertonic saline and may have therapeutic potential for pathological pain [23]. Further reinforcing the MD's multifaceted role, a study by Liu et al. revealed that MD activation by nociceptive stimuli mediates both defensive reflexes and self-caring responses. Critically, chemogenetic activation of the MD or the ACC-MD pathway induced hyperalgesia, aversion, and anxiety-like behaviors, whereas their inhibition alleviated both sensory and emotional comorbidities in neuropathic pain mice [20]. Moreover, neurocircuit studies indicate that the PVT contains anterior and posterior subregions with distinct microcircuit architectures that modulate chronic pain sensitization and its comorbidity with depression disorders [21,22], suggesting that PVT circuits serve as a neural substrate linking sensory and affective symptoms.

The central role of the thalamus in pain processing has prompted it as a therapeutic target for chronic pain. Clinically, approaches such as stereotactic surgery, radiofrequency ablation, and DBS, have focused on specific thalamic nuclei, including the VPL, ventral posteromedial nucleus (VPM), central medial nucleus (CM), and parafascicular nucleus (PF) [24–26]. However, despite encouraging results in preclinical models, clinical trials of thalamic DBS have yielded only modest pain relief, averaging 60% or less [26–28], suggesting translational gaps for chronic pain management. Three persistent challenges underlie this gap. First, theoretical accounts have largely overlooked the dynamic interactions between thalamic sensory and affective circuits, effectively treating these streams as separable rather than integrated. Second, substantial technical barriers in non-invasive neuromodulation limit the ability to target and selectively modulate discrete thalamic nuclei, including those engaged by transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). Third, our understanding of the biophysical and neurophysiological mechanisms underlying neuromodulation remains incomplete, with no consistently defined, standardized, and reproducible stimulation parameters or protocols. Although invasive DBS remains the clinical gold standard for certain indications, its variable efficacy and associated risks limit its broader adoption. Conventional non-invasive techniques, such as transcranial direct/alternating current electrical stimulation (tDCS/tACS), generally lack the spatial specificity needed to selectively modulate thalamic nuclei. Emerging techniques, including transcranial temporal interference stimulation (TIS) [29], focused ultrasound stimulation (FUS) [30], promise greater access to deep brain targets, but face challenges in parameter optimization, reproducibility of dose-response effects, spatial accuracy, and unpredictable neuroplastic adaptations. Taken together, these issues highlight the pressing necessity for next-generation therapies that combine precise anatomical targeting with a mechanistic understanding of thalamic circuits to guide parameter-optimized, evidence-based interventions.

In this narrative review, we synthesize cross-species evidence to: (1) critically reevaluate the dual roles of the thalamus in encoding acute pain and dysregulating chronic pain, with particular emphasis on the integrative functions of MITN as illustrated in Fig. 1; (2) assess contemporary neuromodulation modalities, including DBS, TIS, and FUS as depicted in Fig. 2; and (3) propose a precision neuromodulation framework that bridges anatomical insights with biophysical and neurophysiological mechanisms to inform clinical translation (see Fig. 2). Collectively, these insights could inform a shift toward integrated, network-level management of chronic pain, moving beyond isolated symptom relief, while acknowledging the need for rigorous translational validation (as shown in Fig. 3).

2. Anatomy and functional basis of the thalamus

The thalamus is an evolutionarily conserved, bilaterally symmetrical structure within the diencephalon, comprising approximately 50–60 distinct nuclei [31,32]. Anatomically, the thalamus divides into dorsal and ventral regions: the dorsal thalamus predominantly contains cortical-projecting relay nuclei, whereas the ventral region mainly consists of the reticular thalamic nucleus (RTN), which projects extensively to other thalamic nuclei [33,34]. Most studies narrowly define "thalamus" as the dorsal portion, reflecting its

A Human brain
Rat brain
Thalamus
~10cm
~1cm

B Anterior nucleus
Medial nucleus
Posterior nucleus
Ventral nucleus
Lateral nucleus
Reticular nucleus
Intralaminar nucleus
PT
RE
PVT
MD
P
C
VA
VM
LD
VL
VPI
VPM
VPL
VPM
SG
Purvinar
MGN
LGN
Cingulate gyrus
Prefrontal cortex
Motor cortices
Somatosensory cortex
Posterior association areas
Prefrontal cortex
Auditory cortex
Visual cortex

C VPTN Processes nociceptive information.
MITN Integrates both sensory and affective pain components.
RTN Modulates thalamocortical signaling.
Unknown / not involved in nociception.
Limbic regions
PBN
STT
RTN (Inhibition)
MITN (Excitatory)
VPTN (Excitatory)
PFC, ACC, anterior insula
Primary and secondary somatosensory cortices, posterior insula

(A) Anatomical location of the thalamus in the human and rodent central nervous systems. Situated centrally beneath the cerebral cortex and above the brainstem, the thalamus represents the largest ovoid gray matter structure in the diencephalon. (B) Subnuclear organization and cortical projections of the thalamus. The thalamus comprises seven principal nuclear groups: anterior, medial, lateral, ventral, posterior, intralaminar, and the peripherally located reticular thalamic nucleus. These nuclei establish extensive, specific connections with the cerebral cortex, collectively supporting complex brain functions including sensory perception, motor control, cognition, and consciousness. (C) Functional grouping of thalamic nuclei related to pain processing. Thalamic nuclei implicated in nociception are organized into three functional categories: ventral and posterior thalamic nuclei (VPTN), medial and intralaminar thalamic nuclei (MITN), and the reticular thalamic nucleus (RTN). The VPTN, encompassing portions of the ventral and posterior nuclei, primarily projects to the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), and posterior insula. It mediates discrimination of sensory aspects of nociception, such as intensity and location, and contributes to sensory hypersensitivity observed in chronic pain. The MITN, including segments of the medial and intralaminar nuclei, projects to regions such as the prefrontal cortex (PFC), anterior cingulate cortex (ACC), and anterior insula, where it bidirectionally modulates sensory-affective integration and is involved in affective comorbidities related to pain. The RTN modulates thalamocortical pain signaling through inhibitory control of information transmission from other thalamic nuclei; its projections are mainly intrathalamic, serving as a critical regulatory interface. Note: The figure illustrates selected anatomical projections of thalamic nuclei and does not represent the full complement of their connectivity. **Abbreviations:** AV, anteroventral nucleus; AM, anteromedial nucleus; AD, anterodorsal nucleus; LD, lateral dorsal nucleus; LP, lateral posterior nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VM, ventromedial nucleus; VP, ventral posterior nucleus; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus; VPI, ventroposterior inferior; CM, centromedial nucleus; CL, central lateral nucleus; PF, parafascicular nucleus; PC, paracentral nucleus; MD, mediodorsal nucleus; PT, paratenial nucleus; PVT, paraventricular nucleus; RE, reunions nucleus; LGN, lateral geniculate nucleus; MGN, medial geniculate nucleus; PO, posterior nucleus; SG, supragenicular nucleus; PBN, parabrachial nucleus; STT, spinothalamic tract.

Parkinson's disease [42], essential tremor [43], and a range of other neurological disorders.

2.1. The functional relevance of thalamic nuclei

The thalamus is delineated by the characteristic Y-shaped internal medullary lamina, which partitions it into anterior, lateral, medial, and posterior regions. Current neuroanatomical schemes identify seven principal nuclear groups based on cytoarchitecture and connectivity [44,45]: (1) anterior nuclear group, (2) lateral nuclear group, (3) ventral nuclear group, (4) intralaminar nuclear group, (5) medial nuclear group, (6) posterior nuclear group, and (7) the RTN (as shown in Fig. 1). Notably, the organization of these groups varies considerably across species, particularly among humans, non-human primates, and rodents [46,47], thus underscoring the necessity for species-specific nomenclatures and cross-species referencing frameworks such as BrainInfo (<http://www.braininfo.org>).

The major thalamic nuclear groups serve distinct roles (as illustratively shown in Fig. 1). For a detailed introduction to the structure and function of thalamic nuclei, see Boelens Keun et al. [44].

- (1) The anterior nuclear group, comprising the anteroventral (AV), anterodorsal (AD), and anteromedial (AM) nuclei, supports cognitive processes such as emotional regulation, memory consolidation, and spatial navigation via connections with the subicular cortex, retrosplenial cortex, and mammillary bodies as part of the hippocampal-diencephalic-cingulate network [48–50].
- (2) The lateral nuclear group, including the lateral dorsal (LD) and lateral posterior (LP) nuclei, bridges spatial navigation through hippocampal-cingulate circuits and visuoautonomic integration via inputs from the superior colliculus and visual cortical regions [51–54].
- (3) The ventral nuclear group, encompassing the ventral anterior (VA), ventral lateral (VL), ventromedial (VM), and ventral posterior (VP) nuclei, facilitates motor planning, execution [55,56], and somatosensory processing (e.g., touch, pain, and proprioception) [19,57–59], with somatotopic organization in the VPL and VPM subnuclei [60,61].
- (4) The intralaminar nuclear group, particularly the central lateral (CL) and CM-PF complexes, integrates ascending spinal, brainstem, and cerebellar inputs to modulate consciousness, sensorimotor function, nociception, and cognitive-affective processes via cortico-striatal projections [62–65].
- (5) The medial nuclear group, led by the MD and complemented by midline nuclei (paratenial [PT], PVT, rhomboid (RH) and reuniens [RE]) [45,63,66], links sensory and motor information with prefrontal and limbic regions to support olfaction, gustation [67], nociception [19,21–23,59], visual perception [68], emotion, and executive functions [69,70].
- (6) The posterior nuclear group, which includes the lateral and medial geniculate nuclei (LGN/MGN), pulvinar, suprageniculat (SG), and posterior nuclei (PO), serves as a hub for visual [71–73], auditory [74], and multisensory processing [75], enabling sensory integration and higher-order cognitive functions such as attention and executive control [76,77].
- (7) The RTN is a GABAergic shell-like structure surrounding the lateral thalamus that modulates thalamocortical interactions via topographically organized inhibitory projections to specific thalamic nuclei [78–80]. It integrates multisensory inputs and regulates limbic and motor functions [81–83]. Dysfunction of the RTN has been linked to neurodevelopmental and neurological disorders, including attention deficit hyperactivity disorder, chronic pain, epilepsy, and schizophrenia [81–85].

2.2. Thalamic functional classification and pain-related implications

Traditionally, thalamic nuclei have been classified functionally into three categories: (1) *specific relay nuclei* transmitting modality-specific sensory information (e.g., VPL, VPM, LGN, and MGN), (2) *non-specific nuclei* integrating multimodal inputs and modulating arousal (e.g., intralaminar nuclei), and (3) *association nuclei* supporting cognitive functions via cortico-thalamo-cortical circuits (e.g., ATN and MD) [62,86,87]. More recent frameworks arrange nuclei along a sensory-to-limbic gradient, comprising sensorimotor, limbic, and interface groups that enable cross-domain integration [62,88].

A key principle underlying thalamocortical circuits is their reciprocal connectivity: thalamic neurons project to both middle cortical layer 4 and superficial layers 1–2, receiving afferents mainly from cortical layers 5 and 6 [89,90]. The modern distinction between *first-order* (FO) and *higher-order* (HO) nuclei represents a paradigm shift, moving beyond thalamocortical output-based classifications to define thalamic function by its sources of dominant input within cortico-thalamo-cortical circuits [90,91]. Based on their dominant driving inputs, thalamic nuclei are classified into FO and HO types [91–94]. FO nuclei (e.g., LGN for vision and VPL for somatosensation) receive their primary inputs from subcortical afferents (e.g., retina and spinal cord) and are modulated by layer 6 corticothalamic feedback, functioning as dedicated sensory relays. In contrast, HO nuclei (e.g., pulvinar in vision and PO in somatosensation) are predominantly driven by layer 5 cortical inputs and play a key role in mediating intercortical communication and integrating complex sensorimotor and cognitive signals [39,93,95]. This FO/HO classification is supported by converging lines of evidence that delineate their anatomical, physiological, and functional differences. First, anatomical connectivity: trans-synaptic viral tracing studies have definitively mapped the origin of driver inputs, showing that HO nuclei like the pulvinar receive substantial layer 5 projections from visual cortical areas, whereas FO nuclei like the LGN receive minimal such input [92,96]. Second, synaptic properties: ultrastructural analyses reveal a higher ratio of driver-type to modulatory-type synapses in FO compared to HO nuclei, reflecting their more direct relay function [97,98]. Third, physiological signatures: *in vivo* recordings demonstrate that HO thalamic neurons exhibit distinct firing patterns, such as a higher propensity for burst firing even during alert states, and differential responses to neuromodulation, consistent with their role in integrative and state-dependent processing [99,100]. This body of work collectively moves the field beyond viewing the thalamus as a passive relay, instead highlighting its active, hierarchical role in information

processing. Importantly, this classification is both cross-modal and genetically conserved [101]. This organizational principle is conserved across sensory and non-sensory systems [89], positioning FO nuclei as dedicated sensory gateways and HO nuclei as integrators of cross-cortical communication [93]. At the neuronal level, thalamocortical cells segregate into core-type neurons, which project focally to layer 4, and matrix-type neurons, which diffusely innervate layer 1 [102–104]. While FO nuclei are typically enriched in core cells and HO nuclei favor matrix cells, this relationship is not absolute; both cell types coexist across nuclei, and the FO/HO distinction reflects predominant, not exclusive, connectivity patterns [91,105]. Furthermore, as a multifunctional regulatory hub, the RTN plays a pivotal role in modulating and coordinating information flow between the thalamus and cortex via both FO and HO nuclei [78,82,106]. Its critical function in shaping thalamocortical connectivity should not be overlooked.

In clinical contexts, HO nuclei appear to contribute to pain processing in ways that differ notably from FO nuclei. FO nuclei, such as the VPL, relay somatotopically organized nociceptive input from spinal and brainstem pathways to S1, supporting the sensory-discriminative dimension of pain [58]. Conversely, HO nuclei (e.g., PO and MD), receive substantial cortical and subcortical inputs and integrate multisensory and motor information [107], refining sensorimotor responses and enhancing pain perception [108,109]. The MD nucleus, in particular, modulates affective-motivational components through extensive connections with anterior cingulate and prefrontal cortices, influencing the negative affect associated with pain [18,110]. Collectively, HO nuclei synthesize sensory, motor, and emotional dimensions, with potential implications for pain chronification and its comorbidity with affective disorders, making them promising targets for neuromodulation.

3. Thalamic contributions to pain processing and chronic pain

Pain is a complex, multidimensional experience shaped by distinct yet interacting neural circuits [41,111]. The thalamus serves as a critical relay hub, where ascending nociceptive signals, primarily transmitted through the VPL and MD nuclei, integrate with descending inhibitory pathways such as projections from the prefrontal cortex (PFC) to the brainstem, ultimately influencing pain perception (See Fig. 2) [112]. This processing occurs through two parallel pathways: the lateral pathway, which encodes the sensory and discriminative aspects of pain, or painfulness, and the medial pathway, which mediates the affective and motivational components, often described as suffering [112]. Dysregulation between these thalamic pathways and descending inhibitory control contributes to the emergence of chronic pain [112,113], with thalamic dysfunction playing a pivotal role in both the onset and maintenance of pathological pain states [41,114]. Given its key position within these networks, the thalamus represents a promising target for neuromodulatory therapies aimed at relieving chronic pain.

3.1. Thalamic nociceptive coding in acute pain

Acute pain perception relies on the thalamus to relay and encode nociceptive signals. Although the underlying causes of pain are diverse, most pain episodes begin with the activation of peripheral nociceptors located in tissues such as the skin or joints. These signals are conveyed through two primary types of nerve fibers: the myelinated A δ fibers, which are responsible for the rapid transmission of sharp or immediate "first pain", and unmyelinated C fibers, which transmit slower, more diffuse "second pain" often characterized by a burning sensation [115]. Nociceptive inputs originating from the dorsal root ganglia or trigeminal ganglia are transmitted to specific laminae within the spinal dorsal horn or the brainstem trigeminal nucleus. Within the dorsal horn, particularly in its superficial layers that receive the densest nociceptive input [116,117], primary afferents synapse with secondary neurons that engage three major ascending pathways: the spinothalamic tract (STT), the spinoparabrachial-amygdala pathway (SPA), and the spinoreticulothalamic pathway (SRT). These pathways further diverge into lateral and medial pathways, distinguished by their composition of thalamic nuclei and the projection patterns of the STT [13,41,111]. The STT, which is phylogenetically conserved, serves as the principal route for nociceptive transmission [46]. Most of its axons cross the midline to terminate in contralateral thalamic nuclei, including lateral, posterior, and medial groups, as well as in limbic regions [41]. A smaller number of ipsilateral projections also contribute to bilateral activation of cortical regions [118]. This hierarchical processing is initiated in the cortical areas of the contralateral hemisphere that receive input from the STT [119], and subsequently recruits broader neural networks through thalamocortical loops [120]. Ultimately, these processes support the integration of sensory discriminative and affective motivational components of pain.

Meta-analytic evidence confirms consistent thalamic activation during acute pain [121]. The STT transmits nociceptive input to a range of thalamic targets, spanning the ventral (VPL, VPM, and VPI), posterior (PO, SG, and pulvinar), and medial or intralaminar (MD, PVT, CL, CM, and PF) nuclear groups [13,41,111,112,122]. Notably, each group receives distinct proportions of spinothalamic input, approximately thirty-five percent of fibers terminate in ventral regions, forty percent in posterior nuclei, and the remaining twenty-five percent in medial or intralaminar areas [41]. The VPTN, forming the lateral thalamic network, relay most of these inputs to both primary and secondary somatosensory cortices. This lateral pathway predominantly processes the sensory-discriminative dimensions of pain, including the precise location, intensity, and qualitative characteristics of noxious stimuli. In contrast, the MITN receive comparatively fewer direct projections from the spinothalamic tract but integrate convergent inputs from multiple sources, including the RTN, parabrachial nucleus (PBN), and limbic structures [63,65,123]. These MITN predominantly project to the ACC and PFC, constituting the medial thalamocortical pathway that facilitates the integration of the affective, motivational, and cognitive components of pain. Functional investigations have elucidated pathway-specific specializations: projections from the PBN to the PVT modulate pain-associated negative affect and anxiety-like behaviors, whereas PBN connections to the intralaminar nuclei (ILN) regulate nocifensive reflexes [123,124]. Moreover, distinct parabrachial subnuclei exert specialized roles; the lateral PBN-VPL pathway mediates reflexive defensive behaviors, while medial PBN-MITN projections support adaptive coping mechanisms during

Table 1
Cross-species thalamic plasticity changes in chronic pain pathophysiology.

Species	Thalamic Subregions	Neuroplasticity Changes	Associated Pathologies
Human	Whole thalamus	Reduced thalamic gray matter volume	Chronic back pain [142,143] Chronic neuropathic pain [134–136,146–148] Complex regional pain syndrome [149] Hip osteoarthritis pain [150] Central post-stroke pain [151–153]
	Lateral and posterior nuclei	Thalamic lesions	
	Ventral caudal nucleus		
	Anterior pulvinar nucleus		
	Whole thalamus	Thalamocortical dysrhythmia	Postherpetic neuralgia [135] Chronic low back pain [139]
	Ventral lateral/posterolateral nucleus		
	Medial dorsal/ventral medial nucleus		
Rodent	VPTN	Ventral posterolateral nucleus (VPL)	Enhanced VPL ^{Glu} activities and projections to S1HL ^{Glu} , and dysregulation of HCN2 channels in VPL
	VPTN	Posterior nucleus (PO)	Loss of presynaptic GABAergic projections to PO
			Enhanced projections from ventral ZI PV ⁺ neurons to PO
			Enhanced projections from the PO ^{Glu} to S1HL ^{Glu}
			Enhanced projections from the S2 ^{Glu} to VPL and PO
	VPTN	VPL and PO	Enhanced MD ^{Glu} neuronal activities
	MITN	MD	Enhanced MD ^{Glu} neuronal activities
			Increased spontaneous and evoked activities in MD
			Enhanced AMPA receptor-silent glutamatergic synapses-mediated projections from MD to ACC
			Enhanced projections from MD to ACC
			The MD and ACC-MD pathway
			The M1-MDL-NAC circuit
			The PFC-MD pathway
		Paraventricular nucleus (PVT)	aPVT Enhanced projections from aPVT to CeA
			Inhibition of glutamatergic neurons in aPVT, combined with systemic ketamine
			The projection from aPVT to BLA (<i>Cacna1e</i> upregulation)
		pPVT	Hyperactivity of pPVT ^{Glu} -CeA-vIPAG ^{Glu} circuit
			The projection from pPVT to CeA (<i>Grin2a</i> expression)
			The vIPAG-CM-BLA circuit
	Central medial nucleus (CM) Parafascicular nucleus (PF)		Enhanced inhibition of CeA ^{GABA} -PF ^{Glu} -S2 circuit
			The PF ^{Glu} -ACC ^{GABA} -Glu circuit
			The projection from RTN to VPL/VPM
			Enhanced burst firing of RTN neurons
	Reticular thalamic nucleus (RTN)		Increased deposition of perineuronal nets around GABAergic interneurons in RTN

Abbreviation: VPTN, ventral and posterior thalamic nuclei; MITN, medial and intralaminar thalamic nuclei; S1HL, the hindlimb primary somatosensory cortex; ZI, zona incerta; S2, the second somatosensory cortex; ACC, anterior cingulate cortex; MDL, the lateral part of mediodorsal nucleus; NAC, nucleus accumbens; PFC, prefrontal cortex; aPVT, anterior paraventricular nucleus; pPVT, posterior paraventricular nucleus; CeA, central nucleus of amygdala; vIPAG, ventrolateral periaqueductal gray matter; BLA, basolateral amygdala; LHB, lateral habenula; Glu, glutamatergic; PV⁺, parvalbumin (PV)-positive neuron; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; GABA, gamma-aminobutyric acid; HCN2, hyperpolarization-activated cyclic nucleotide-gated.

persistent pain states [125]. This model thus illustrates the thalamus's role in converging heterogeneous nociceptive inputs via multiple parallel streams, which collectively shape the multifaceted nature of pain perception.

Classical models of thalamic pain processing have traditionally posited a clear functional segregation: the lateral thalamus predominantly mediates sensory-discriminative aspects of pain, whereas the medial thalamus governs its affective-motivational components. Contemporary evidence, however, reveals a more integrated thalamic architecture that refines this classical view. For instance, the lateral thalamic nuclei, including the VPL and VPM nuclei, are enriched with wide dynamic range neurons that integrate convergent somatosensory inputs (tactile, proprioceptive, and nociceptive). Through their firing dynamics, these neurons contribute to encoding and discriminating nociceptive versus non-nociceptive inputs, thereby shaping the sensory qualities of pain [126–128]. In contrast, medial thalamic nuclei (e.g., MD and CM-PF) demonstrate stronger nociceptive-specific neuronal responses [129], consistent with their established role in affective-motivational processing. Emerging evidence further indicates that medial thalamic neurons can exhibit dual coding, representing both stimulus intensity (sensory dimension) and aversive valence (affective dimension) [18,19,23,110,130–133]. Cross-species studies from our group indicate that the MD nucleus preferentially encodes noxious input, with tactile stimuli eliciting comparatively weaker responses [19]. The functional coupling between the MD and the ACC during pain processing provides mechanistic basis for this specialization [19]. This is supported by rodent lesion studies, wherein MD disruption modulates both nociceptive sensitivity [23] and associated affective behaviors [133]. Collectively, these findings extend the traditional framework by underscoring a greater degree of specificity within the medial pathway and re-emphasizing the integrated relationship between the sensory and affective components of pain. This medial pathway specificity likely stems from heightened nociceptive-specific neuronal responses and the integration of diverse cortical and subcortical inputs, which enhances the discrimination between painful and non-painful stimuli while preserving the lateral pathway's primary role in sensory discrimination.

3.2. Thalamic reorganization in chronic pain pathophysiology

In chronic pain, the thalamus undergoes substantial functional reorganization, shifting from its role as a simple relay for nociceptive signals during acute pain. Yet, the mechanisms driving this transition remain largely elusive. Structural magnetic resonance imaging (sMRI) investigations have consistently reported negative correlations between thalamic volume and both pain intensity [134,135] and pain duration [136]. Complementing these findings, resting-state functional MRI (fMRI) studies reveal disrupted functional connectivity patterns linking the thalamus with widespread cortical and subcortical regions [135,137–139]. However, conventional neuroimaging approaches, particularly standard MRI, lack the spatial precision necessary to capture neuroplastic alterations at the level of individual thalamic subnuclei. Consequently, many studies are compelled to treat the thalamus as a uniform entity, overlooking its complex subnuclear architecture detailed by recent high-resolution thalamic nuclei segmentation atlases and connectomic roadmaps [140,141]. This methodological constraint poses a major barrier to clinical translation, as it obscures the distinction between adaptive neuroplastic compensation and maladaptive pathological remodeling within thalamocortical circuits. Emerging evidence from rodent models, employing intersectional strategies that combine viral pathway tracing with cell-type specific manipulations, underscores the urgency of conducting complementary human studies. Such investigations should integrate advanced segmentation methodologies alongside ultra-high-field imaging to unravel the nuanced thalamic reorganization in chronic pain.

Human neuroimaging studies have frequently associated chronic back pain (CBP), particularly neuropathic subtypes, with reductions in thalamic gray matter volume [142]. These findings have been corroborated by longitudinal investigations [143], reinforcing the centrality of the thalamus in pain-related neural reorganization. However, the literature also reveals inconsistencies. Some studies report increased thalamic volume, primarily within the left hemisphere [144], while others found no significant volumetric alterations in CBP cohorts [145]. These discrepancies likely stem from heterogeneity in patient populations, pain chronicity, and methodological differences. In contrast to the mixed findings in CBP, thalamic atrophy is a more consistent feature across chronic pain conditions. Volume reductions have been robustly demonstrated in neuropathic pain [134–136,146–148], complex regional pain syndrome [149], and hip osteoarthritis pain, where surgical intervention can partially reverse these volumetric changes [150]. Furthermore, clinical data link post-stroke central pain to focal structural damage to specific thalamic nuclei, particularly the ventral caudal and anterior pulvinar nuclei [151–153].

Beyond structural alterations, chronic pain is characterized by distinct thalamocortical connectivity changes. For instance, in postherpetic neuralgia, there is increased thalamic coupling with the S1 and S2, which contrasts with reduced connectivity to the periaqueductal gray (PAG) and prefrontal areas [135]. Similarly, chronic low back pain is associated with thalamic subregion-specific dysconnectivity: the VL and VPL nuclei exhibit enhanced connectivity with the postcentral gyrus, while the MD and VM nuclei show reduced connectivity to the insula [139]. These patterns suggest that chronic pain may arise from disrupted equilibrium between ascending (thalamocortical) and descending (corticothalamic) pathways, or from a functional imbalance between lateral (sensory-discriminative) and medial (affective-motivational) thalamic nuclei. Moreover, the medial thalamic nuclei, particularly the MD nucleus, play a multifaceted role in the pathophysiology of chronic pain. Aberrant connectivity between the MD nucleus and limbic-affective processing regions, such as the amygdala, anterior insula, and medial PFC, has been reported in chronic migraine [154], thalamic pain [155], and chronic knee pain [156]. This network-level dysregulation may underpin the frequent comorbidity between persistent pain and negative affective states (Table 1).

Unlike human neuroimaging studies, which primarily reveal correlational changes in thalamocortical connectivity without establishing causality, rodent pain models offer more definitive evidence linking thalamic circuits to chronic pain mechanisms. Utilizing techniques such as optogenetics, chemogenetics, and electrophysiology, animal studies have successfully dissected the distinct functional roles of individual thalamic nuclei. For example, research has demonstrated that the VPTN (e.g., VPL and PO) mediate sensory hypersensitivity [109,157,158], the MITN (e.g., MD and PVT) regulate the interplay between sensory and affective pain

components [21,110,133], and the reticular thalamic nucleus (RTN) dynamically gates thalamocortical pain signaling [159,160]. These circuit-level interventions in rodents provide mechanistic insights that extend beyond the correlational human data, elucidating thalamic function across synaptic, cellular, and network levels within pain pathology.

3.2.1. Ventral and posterior thalamic nuclei (VPTN): roles in sensory hypersensitivity

The VPTN, primarily comprising the VPL and PO nuclei, mediate sensory hypersensitivity in chronic pain through bidirectional thalamocortical-corticothalamic circuits (Table 1). The excitatory glutamatergic pathway from the VPL to the S1 underlies sensory abnormalities; for instance, dysregulation of hyperpolarization-activated cyclic nucleotide-gated channel 2 (HCN2) in the VPL directly contributing to pain hypersensitivity in mice [157,158,161]. In spinal cord injury (SCI) models, disrupted GABA receptor-mediated presynaptic inhibition of inputs to the PO nucleus heightens its excitability, thereby intensifying pain-related behaviors [108]. Furthermore, parvalbumin-positive (PV+) interneurons in the zona incerta (ZI) modulate PO activity to amplify nociceptive sensitization [162], while its glutamatergic projections from the PO to S1 specifically regulate hypersensitivity induced by tissue injury [109]. Collectively, these findings demonstrate a functional convergence of VPL and PO circuits in shaping somatosensory cortical connectivity, primarily affecting the sensory-discriminative rather than the affective dimensions of pain.

At the cortical level, neurons in layers 5 and 6 of S1 exert distinct and contrasting influences on pain through separate corticothalamic pathways. Glutamatergic projections from S1 layer 6 to the VPL amplify thalamic sensory responses and facilitate inflammatory pain, while simultaneously suppressing layer 5 neuronal activity. Conversely, projections from S1 layer 5 to the VPL mediate descending inhibition to attenuate sensory hypersensitivity [163]. Beyond S1, the adjacent S2 also contributes to pain perception and its modulation. Deep-layer glutamatergic neurons in S2 form monosynaptic connections with VPL and PO nuclei and exhibit pathological hyperactivity under neuropathic pain conditions, implicating them in the maintenance of chronic pain [164]. Optogenetic silencing of either these S2 glutamatergic neurons or their projections to VPL/PO nuclei alleviates mechanical allodynia and thermal hypersensitivity in neuropathic models, without altering affective pain components [164]. Additionally, projections from the auditory cortex to VPL/PO mediate sound-induced analgesia, and inhibition of these pathways reverses inflammatory pain [165]. In summary, the VPTN and its integrated thalamocortical-corticothalamic circuits as pivotal mediators of sensory hypersensitivity in chronic pain, emphasizing their integral role in processing and modulating nociceptive signals.

3.2.2. Medial and intralaminar thalamic nuclei (MITN): roles in pain and affective comorbidities

The MITN, mainly comprising the MD, PVT, and CM-PF nuclei, function as critical hubs for integrating the sensory and affective dimensions of pain (Table 1). These nuclei process convergent somatosensory and affective information to shape both the perceptual and emotional responses to pain, with accumulating evidence underscoring their pivotal role in chronic pain. The MD nucleus is a critical hub within this network [20,133]. Pharmacological inhibition or lesioning of the MD markedly attenuates mechanical and thermal hyperalgesia in spared nerve injury (SNI) [166] and modulates mechanical sensitivity in muscle pain models [23]. Furthermore, in SCI models, MD neurons exhibit heightened spontaneous firing and amplified responses to noxious stimuli [129]. Emerging evidence suggests functional specialization within MD subregions. For instance, the lateral subregion of the MD appears more specifically associated with the emotional aspects of pain [133]. Casually, glutamatergic projections from the MD to the ACC drive mechanical allodynia through synaptic plasticity [167]. Optogenetic stimulation of the MD-ACC pathway exacerbates aversive behaviors in neuropathic pain models, whereas its inhibition reduces pain-related avoidance in mice [18]. Complementing these findings, chemogenetic activation of either the MD or the ACC-MD pathway induces hyperalgesia alongside aversion and anxiety-like behaviors. Conversely, inhibiting this corticothalamic circuit alleviates both pain and emotional comorbidities in neuropathic mice, providing a mechanistic basis for developing neuromodulation therapies against refractory neuropathic pain [20]. The MD also anchors broader circuits that govern the emotional and cognitive aspects of pain. A pathway connecting the primary motor cortex (M1), MD, and nucleus accumbens (NAc) regulates pain-related negative emotions and coping strategies [168]. Additionally, projections from the PFC to the MD mediate the overlap between chronic pain and fear-related affective states [110]. Thus, the MITN, with the MD nucleus as an important node, acts as an integrative hub that translates sensory input into coordinated affective and behavioral pain responses.

The PVT, comprising anterior (aPVT) and posterior (pPVT) subdivisions, modulates chronic pain through distinct, topographically organized pathways. Glutamatergic projections from the aPVT to the central amygdala (CeA) regulate baseline pain sensitivity and contribute to mechanical allodynia observed in both neuropathic and inflammatory pain models [169]. Notably, simultaneous inhibition of aPVT glutamatergic neurons alongside systemic ketamine administration alleviates both sensory and affective symptoms, suggesting a promising approach for treating pain-depression comorbidity [21]. Conversely, the pPVT promotes neuropathic pain sensitization via its descending projections to the CeA and ventrolateral periaqueductal gray (vlPAG) [22]. Recent data further delineate these functional subdivisions: glutamatergic aPVT neurons, projections to the basolateral amygdala (BLA), co-regulate visceral pain and anxiety through upregulation of *Cacna1e* gene, whereas pPVT neurons influence anxiety selectively through direct CeA projections dependent on *Grin2a* gene expression [170]. In summary, the PVT employs segregated anterior-posterior circuits to differentially mediate the sensory and affective dimensions of pain, thereby illuminating the neural basis of pain-affective comorbidities and revealing precise molecular targets for intervention.

The CM-PF complex, although less extensively studied than other MITN nuclei, serves a dual function in nociceptive and affective processing. Chemogenetic inhibition of the CM nucleus alleviates mechanical allodynia in neuropathic pain, implicating a specific vlPAG-CM-BLA circuit in nociceptive transmission [171]. Parallely, a CeA-PF-S2 circuit, comprising GABAergic CeA inputs to the PF and subsequent glutamatergic transmission to the S2, mediates depression-related pain phenotypes [172]. Disruption of this pathway alleviates both nociceptive hypersensitivity and affective impairments in chronic pain models. Additionally, glutamatergic projections

from the PF to the ACC have been shown to modulate depressive-like behaviors [109]. Clinically, the CM-PF complex is a validated DBS target for chronic pain [173,174], highlighting its therapeutic potential for concurrently addressing pain perception and comorbid emotional disturbances.

3.2.3. Reticular thalamic nucleus: dynamic control of thalamic pain processing

The RTN acts as a crucial inhibitory hub within thalamocortical networks, exercising precise control over pain processing through its extensive GABAergic projections to multiple thalamic nuclei [81,160,175] (Table 1). Notably, RTN fibers projecting to the ventral thalamic complex (VT) selectively target the VPL and VPM nuclei, a circuit that shapes thermal hyperalgesia in chronic inflammatory pain models [160]. Subsequent research has clarified that these same RTN-VT connections are also essential mediators of hyperalgesia induced by chronic sleep disruption, with N-arachidonoyl dopamine (NADA) signaling identified as a key molecular mechanism [175]. Parallel investigations in neuropathic pain models suggest that pathological changes in RTN neuronal activity, particularly enhanced burst firing, may contribute to the commonly observed comorbidity between neuropathic pain and sleep impairments [159]. Furthermore, both inflammatory stimuli and peripheral nerve injury can trigger structural remodeling within the RTN, marked by denser perineuronal net (PNN) deposition around GABAergic interneurons [176,177]. This adaptive change in the extracellular matrix appears to promote pain chronification and lower thresholds to both mechanical and thermal stimuli [176,177]. Altogether, these findings highlight the RTN's GABA-mediated inhibitory influence as fundamental to pain modulation and its associated comorbidities, reinforcing its pivotal role in the neurobiology of chronic pain.

4. Precision thalamic neuromodulation for chronic pain management

Chronic pain remains a challenging neurological disorder, often refractory to conventional pharmacotherapies and demands innovative neuromodulation strategies [6,178]. Emerging evidence indicates that targeted modulation of thalamic nuclei and their circuits can substantially reshape pain perception and reduce related symptoms, including hypersensitivity, allodynia, and comorbid anxiety or depression [21,23,24,30,109,173]. By directly engaging thalamic pathways, these strategies present notable advantages over systemic medications, particularly in lowering risks of opioid dependency, metabolic side effects, and unintended pharmacological actions [179]. Despite these potential, current neuromodulation techniques face substantial barriers to effectively modulating thalamic structures that are central to pain processing. Non-invasive techniques, such as tDCS and TMS, are constrained by fundamental biophysical trade-offs between depth penetration and spatial resolution [180]. Consequently, while effective for modulating cortical excitability, their restricted depth means thalamic nociceptive circuits are largely inaccessible. In contrast, invasive procedures like DBS can reach these subcortical targets but often yield variable outcomes in chronic pain management [7]. The variability in DBS efficacy may reflect the distributed nature of pain networks, where multiple nodes contribute to its multidimensional characters [28]. The limitations of current technologies underscore the need for refined neuromodulatory approaches capable of selectively engaging specific thalamic subcircuits and subnetworks [45]. Future strategies could be designed to address the multifaceted nature of pain, while also overcoming the technical constraints of existing systems. Progress in this area will depend on the innovative integration of advanced neuroimaging, computational modeling, and closed-loop neuromodulation to optimize outcomes for individuals living with chronic pain.

4.1. Technological advances and clinical translation

DBS is a well-established invasive neuromodulation technique employed in both movement disorders and chronic pain treatment. It involves the stereotactic implantation of electrodes into deep brain structures implicated in disease pathology, such as the subthalamic nucleus (STN) [181], sensory thalamus (e.g., VPL and VPM), parts of the intralaminar nuclear (i.e., CM-PF), and PAG [7,24]. An implanted pulse generator delivers controlled electrical stimulation to modulate both localized and distributed neural networks [182]. However, a key limitation of traditional DBS for pain has been its relatively coarse spatial resolution, often treating entire thalamic nuclei as uniform targets. This lack of subdivision precision is a plausible explanation for its inconsistent long-term efficacy, with average pain relief rates ranging from 40% to 60% [28]. Moreover, none of the currently targeted sites provide comprehensive or sustained relief for the majority of chronic pain patients [24,28], partly because the intricate functional micro-architecture of thalamic subnuclei is not adequately engaged. The therapeutic mechanisms underlying DBS are multifactorial, encompassing local and network-level effects that induce neuroplastic changes across diverse spatial and temporal scales [183,184]. At a granular level, DBS modulates neurochemical signaling and fosters neuroplasticity, evident in synaptic remodeling of individual neurons, altered neural oscillations in target regions, and the reorganization of large-scale neural circuits [184]. Furthermore, DBS influences neurotrophic factors and metabolic processes that are vital for neural function and recovery [182–184]. Despite its risks and variable outcomes, DBS remains a gold standard for refractory pain because it provides direct neural interfacing that enables precise programming of stimulation parameters and decades of clinical validation [185,186]. Consequently, the persistent challenges of surgical risk and inconsistent pain relief require efforts to develop safer, non-invasive neuromodulatory alternatives.

The pursuit of precision has become a major impetus for innovation in non-invasive technologies capable of targeting specific thalamic subregions. TIS has revolutionized electrical neuromodulation by addressing the trade-off between stimulation intensity and spatial resolution. This technique utilizes two high-frequency alternating electric fields (f_1 and f_2 , typically within the 1–10 kHz range) to generate a low-frequency envelope ($f_2 - f_1$), enabling selective activation of neurons in deep brain regions while minimizing stimulation of superficial tissues [180,187]. Consequently, TIS facilitates precise, non-invasive modulation of deep nuclei in both humans and animals [188–190], establishing itself as a powerful tool for pain treatment. For instance, recent proof-of-concept studies

have successfully targeted the human VPL nucleus to modulate perceived heat pain, demonstrating the feasibility of influencing sensory-discriminative thalamic circuits without surgery [29]. In parallel, ultrasonic neuromodulation has emerged as another powerful tool [191]. While high-intensity focused ultrasound (HIFU) is used for precise thermal ablation, transcranial low-intensity focused ultrasound (LIFUS) provides reversible, spatially precise neuromodulation by mechanically altering neuronal excitability without damage [192,193]. This millimeter-scale resolution is essential for probing distinct thalamic nuclei. For example, a seminal primate work demonstrated that applying low-intensity FUS to the CM, MD, and VL thalamic nuclei during heat stimulation of the hand significantly suppresses nociceptive BOLD responses and disrupts thalamocortical network connectivity [30]. This finding highlights the potential for ultrasound to dissect the functional contributions of specific medial and intralaminar nuclei to pain affect and salience. In addition, microwave brain stimulation (MBS) has emerged as an additional non-invasive modality with potential to modulate deep brain activity [194,195]. In a typical setup, an antenna or antenna array focuses electromagnetic waves in the GHz range onto a specific target within the near-field region [196]. This method provides greater penetration depth than conventional transcranial electrical stimulation [195], showing potential for targeting thalamic nuclei involved in pain processing. However, the application of MBS in neuromodulation remains at an early stage of development. Interested readers are referred to the comprehensive review by Pereira et al. for further technical and physiological details [195]. Together, TIS and FUS exemplify the ongoing innovation in non-invasive, deep brain neuromodulation, and represent promising alternatives to DBS for managing chronic pain [29,30,197,198] (Fig. 2).

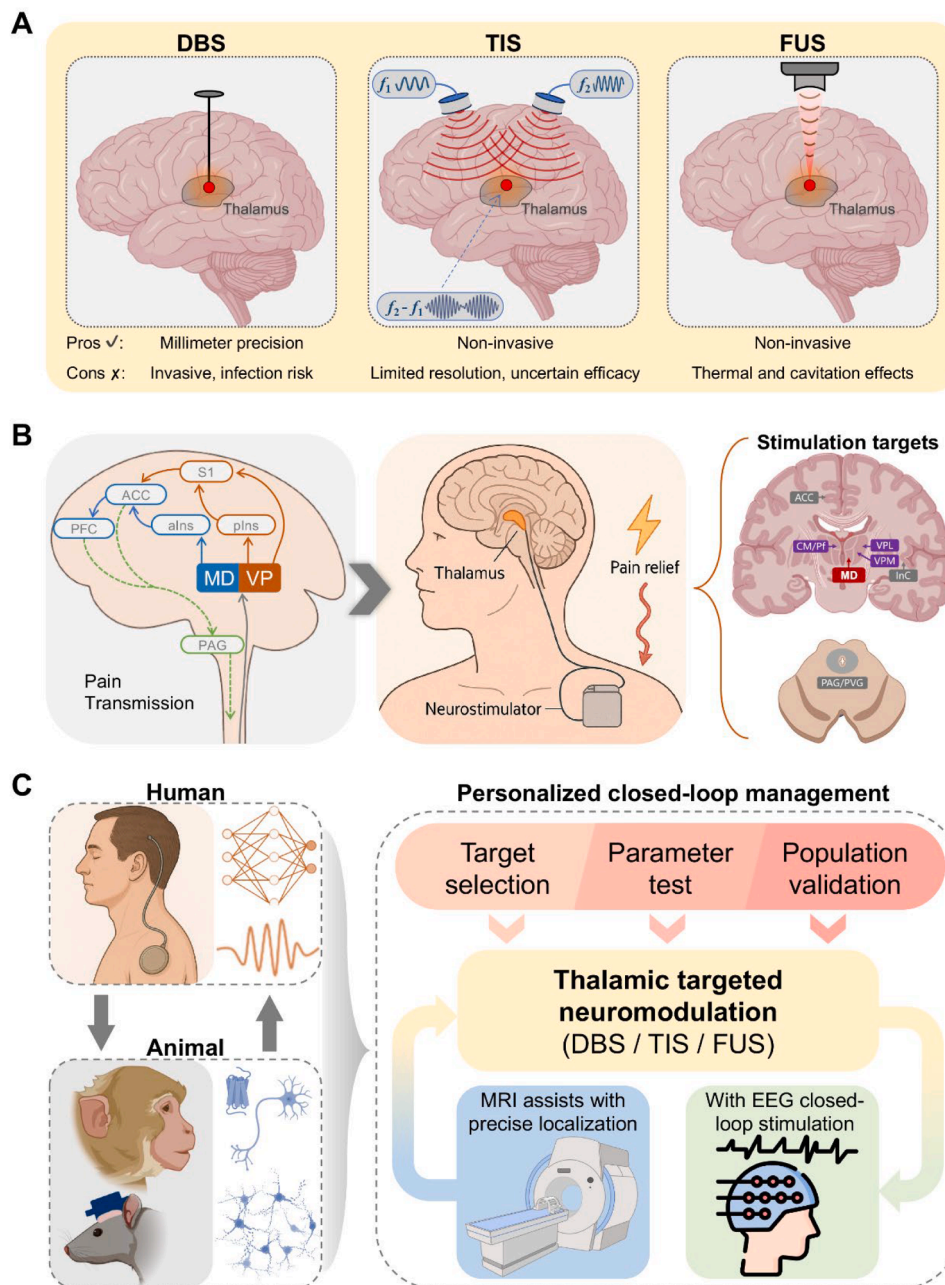
4.2. Integrated applications of non-invasive techniques

The distributed nature of chronic pain necessitates multi-target neuromodulation strategies, but their successful implementation relies on thalamic precision. Recent advances in TIS have expanded its capabilities from single-target to multi-target engagement. These strategies primarily include: (1) using multiple electrode pairs to synchronize stimulation across different network nodes (e.g., the frontoparietal network) [199]; (2) delivering high-frequency currents at different frequencies through a single electrode pair to elicit multi-target effects without additional hardware [200]; and (3) employing multi-electrode carrier currents to generate overlapping amplitude-modulated envelopes, thereby enhancing spatial focality while maintaining stimulation intensity [201]. For chronic pain, this could enable the simultaneous and differential modulation of interconnected thalamic subregions, for example, suppressing hyperactivity in the VPL while normalizing connectivity of the MD nucleus with limbic regions. Such a coordinated approach could more effectively disrupt the maladaptive networks that sustain chronic pain [202]. Compared to TIS, FUS inherently offers superior spatial resolution (millimeters versus centimeters) and deeper penetration, making it exceptionally well-suited for targeting small, deep thalamic nuclei. However, both techniques face the considerable challenge of delivering focused energy reliably through the skull, with efficacy influenced by individual anatomical factors like skull morphology and brain geometry. Research indicates that the efficacy of tES varies with demographic factors such as age, sex, and ethnicity, likely reflecting underlying differences in brain physiology [203]. Though FUS is less sensitive to brain geometry, its energy transmission and focus are still influenced by variations in cranial bone structure [204]. These observations highlight the critical need for individualized approaches, leveraging population-specific computational models and imaging guidance to optimize stimulation parameters in both TIS and FUS applications.

Future progress will likely come from integrating the complementary strengths of these technologies. TIS excels at modulating distributed network dynamics, while FUS provides unparalleled focal precision at the subnuclear level. Combining these approaches with multimodal neuroimaging, such as electroencephalography (EEG) for capturing temporal dynamics and fMRI for spatial guidance, could facilitate the creation of advanced closed-loop neuromodulation systems. Such systems would allow real-time adjustments based on neural activity, enhancing both accuracy and adaptability. Preclinical studies in rodents support this potential, demonstrating that neurophysiological signals can detect pain episodes and trigger targeted neuromodulation, including optogenetic stimulation or DBS resulting in measurable pain relief [205,206]. Although laboratory and case studies have identified various neuroimaging biomarkers, like gamma band oscillations in central and prefrontal regions via scalp EEG [207,208] and delta oscillations within the intracranial orbitofrontal cortex [209], clinically validated and reliable markers for neurofeedback and closed-loop control remain limited. The critical next step is to identify robust, clinically validated neural biomarkers, such as specific oscillatory patterns in thalamocortical circuits that can serve as control signals for these systems. Although DBS remains the cornerstone for severe refractory pain, the ongoing refinement of non-invasive neuromodulation is poised to broaden the therapeutic landscape, particularly for patients unsuitable for surgery. This progress points toward a future in which adaptive, minimally invasive neuromodulation may substantially enhance clinical outcomes for chronic pain management.

4.3. Toward precision targeting of thalamic nuclei

Despite the established centrality of the thalamus in pain processing, clinical neuromodulation strategies targeting this structure continue to face persistent obstacles. Current approaches are often conceptualized within classical medial-lateral dichotomies that require refinement, have yet to fully integrate the sensory and affective dimensions of pain, and lack validated non-invasive modalities for focal thalamic engagement. These gaps hinder therapeutic progress, even as recent breakthroughs highlight the thalamus's potential, particularly the MITN as a key hub for pain regulation. For example, recent evidence demonstrates that chemogenetic activation of the MD or the ACC-MD pathway induces hyperalgesia, aversion, and anxiety-like behaviors. Conversely, inhibiting these same structures alleviates both pain and emotional comorbidities in mouse models of neuropathic pain [20]. In parallel, high-frequency DBS targeting the MD nucleus effectively attenuates pain sensitivity across rodent models of acute, inflammatory, and neuropathic pain in rats [210]. These preclinical findings, however, underscore a pivotal yet under-specified question for clinical



(caption on next page)

Fig. 2. Current status and emerging directions in thalamic-targeted neuromodulation for pain management.

(A) Contemporary approaches to thalamic neuromodulation include deep brain stimulation (DBS), transcranial temporal interference stimulation (TIS), and focused ultrasound stimulation (FUS). DBS enables precise, millimeter-scale targeting of specific thalamic nuclei, but its invasive nature introduces risks such as infection and surgical complications. In contrast, TIS and FUS offer non-invasive alternatives; however, TIS currently faces limitations in spatial resolution and its effectiveness in chronic pain remains under investigation. FUS, while promising, may induce thermal or cavitation effects, underscoring the need for continued safety evaluation. (B) The thalamus functions as a critical hub within cerebral pain networks. Medial thalamic nuclei (e.g., the mediodorsal nucleus, MD) and ventroposterior nuclei (VP; including the ventroposterolateral nucleus, VPL) project to regions such as the anterior insula (aIns), anterior cingulate cortex (ACC), posterior insula (pIns), and primary somatosensory cortex (S1). These connections form ascending pathways that transmit both sensory and affective components of pain. Additionally, the prefrontal cortex (PFC) exerts top-down inhibitory control via projections to the midbrain periaqueductal gray (PAG), creating descending pathways that modulate pain perception. As a result, the thalamus remains a principal target for neuromodulatory treatments, most notably through DBS, where conventional targets include the VPL, ventroposteromedial nucleus (VPM), and centromedian-parafascicular (CM-PF) complex. Recent work points to medial and intralaminar nuclei, such as the MD, as emerging potential candidates for intervention. (C) A precision- framework for thalamic neuromodulation integrates both invasive methods (DBS) and non-invasive techniques (TIS, FUS) to harness the therapeutic potential of diverse thalamic nuclei. Translational success will depend on cross-species studies, spanning human and animal models, to delineate effective targets and optimize stimulation parameters across both healthy and patient populations. High-resolution MRI-guided targeting, informed by detailed thalamic atlases and pain-relevant neuroimaging biomarkers (e.g., gamma-band oscillations detected by EEG), is pivotal for developing closed-loop systems tailored to individual pain profiles. This combined approach has the potential to advance personalized neuromodulation and improve outcomes for patients with chronic pain.

translation: under what pain conditions or symptom dimensions should thalamic activity be enhanced versus suppressed to yield therapeutic benefit? The functional consequence of neuromodulation is not intrinsic to a given nucleus but is fundamentally state-dependent. We propose that the choice between excitatory and inhibitory modulation should be guided by the nature of the circuit dysfunction within the targeted symptom domain. In the context of chronic pain, the thalamus often exhibits a shift toward hyperexcitability. Therefore, inhibitory modulation, typically achieved via techniques such as high-frequency DBS, TIS, or FUS, constitutes a primary strategy [211–213]. This approach is well-suited for normalizing hyperactivity in sensory nuclei like the VPL to alleviate sensory hypersensitivity [25], and equally applicable to affective nuclei within the MITN, such as the MD or PVT nuclei, to counteract their overactivity in driving pain-related emotional disorders. Conversely, excitatory modulation, often induced by low-frequency DBS, TIS, or FUS, finds its rationale in a different therapeutic goal: to potentiate endogenous pain-inhibitory pathways. This strategy may involve targeting nuclei with known antinociceptive functions, such as the VM nucleus, to enhance their descending inhibitory drive [214]. Furthermore, exciting specific thalamic circuits could be designed to boost the activity of endogenous opioid systems, thereby leveraging the thalamus's own analgesic mechanisms. Thus, the choice between excitation and inhibition is not fixed for a nucleus, but a dynamic decision based on whether the therapeutic intent is to suppress a maladaptive gain-of-function or to augment a compensatory or inherent loss-of-function in pain control.

Given the thalamus's abundance of endogenous opioid receptors and the MITN's unique pain-modulatory capabilities [114,215], considerable untapped potential exists for cross-species translatable neuromodulation. Consequently, achieving true precision targeting requires not only spatial localization but also a functional state diagnosis to guide the appropriate modulation mode. Techniques such as TIS and FUS directed at thalamic targets are poised to enable precise and non-invasive pain interventions. Crucially, different neuromodulation techniques (e.g., DBS, TIS, and FUS) and their parameters exhibit inherent biases in their network effects (toward net excitation or inhibition), necessitating that the choice of technology and its parameters be aligned with the therapeutic objective derived from the pathophysiological state, as outlined above. The integration of these techniques with advanced tools, such as thalamic activity-guided closed-loop systems [59], neuroimaging-based pain biomarker monitoring [216], and dynamic brain network modulation [217], may not only clarify core pain mechanisms but also guide the development of individualized analgesic therapies. Explicitly addressing this mode selection problem, determining whether to excite or inhibit a circuit based on individual pathophysiology, is thus critical for enhancing the mechanistic clarity and clinical applicability of the proposed thalamic framework. This multifaceted strategy addresses the need for more precise pain targets and holds strong promise for establishing personalized, mechanism-driven approaches to pain management.

5. Challenges and future directions

5.1. Challenges in thalamic-targeted neuromodulation for chronic pain

The traditional view of the thalamus as a passive sensory relay has shifted. Current research shows it plays an active role in integrating multiple dimensions of pain processing, especially within the MITN, such as the MD, PVT and CM-PF nuclei. This evolving understanding is supported by three key findings: (1) imaging studies reveal gray matter loss and disrupted thalamic connectivity in chronic pain patients [135–137,139,217]; (2) animal experiments link MITN circuit remodeling to both heightened pain sensitivity and affective symptoms [18,20–22,109,133,170]; and (3) clinical observations indicate impaired thalamic integration across sensory, emotional, and cognitive functions in chronic pain [218,219]. Despite these advances, translating such insights into effective neuromodulation remains challenging.

The thalamus is a challenging target due to its deep location and complex organization. It consists of numerous distinct nuclei with overlapping microcircuits and specialized populations, each contributing to different aspects of pain. This organizational complexity gives rise to four interconnected core challenges that currently limit therapeutic efficacy (Fig. 3):

- (1) *Inadequate targeting precision*: The anatomical boundaries between thalamic nuclei are often poorly delineated, hindering accurate and selective engagement. Non-invasive methods like TIS, and FUS currently lack the requisite spatial resolution to isolate adjacent nuclei [220], while invasive DBS entails unavoidable risks of collateral damage to proximate structures.
- (2) *Undefined stimulation parameter space*: Identifying optimal stimulation parameters represents a critical and under-addressed challenge. The efficacy of both invasive (DBS) and non-invasive (TIS, FUS, and MBS) techniques depends on a multidimensional parameter space, where stimulation frequency and waveform are particularly influential [195,204,221–224]. Evidence from other neural circuits indicates that fixed DBS parameters are inadequate. Composite parameters that combine pulse width, amplitude, and frequency outperform frequency alone in predicting DBS outcomes for parkinson's disease [225], while waveform shape (e.g., sinusoidal versus rectangular) substantially influences net neural activation [222,223]. Recent work demonstrates that specific DBS waveforms, including low-frequency symmetric and high-frequency asymmetric biphasic, bidirectionally modulate ACC pyramidal neuron activity and depressive-like behaviors in rodent models [213]. For non-invasive techniques, waveform design broadens the parameter space and holds promise for more efficient deep-brain modulation. Unlike conventional TI, which uses sine-wave carriers to generate amplitude-modulated envelopes, pulse-width modulated TI employs square-wave carriers to realize pulse-width modulation, enabling selective engagement of deep structures without increasing peak field amplitudes [224]. These findings indicate that a range of stimulus parameters shapes neural modulation, highlighting the need for a multi-parameter optimization framework to realize precise targeting of thalamic nuclei and their networks.
- (3) *Translational barriers from species differences*: The translational gap between animal models and human patients is widened by profound interspecies differences in thalamic anatomy, neurochemistry, and functional connectivity. These discrepancies complicate the direct extrapolation of neuromodulation targets, parameters, and mechanisms, as a protocol optimized in rodents may not engage homologous neural populations or produce analogous network effects in the human brain. This is especially pertinent for HO nuclei (e.g., MD), where anatomical boundaries are less conserved and connectivity with associative prefrontal-limbic networks exhibits distinct topological patterns in humans [70,226]. Consequently, a nucleus considered functionally analogous based on animal data may occupy a different position within the human pain processing network.

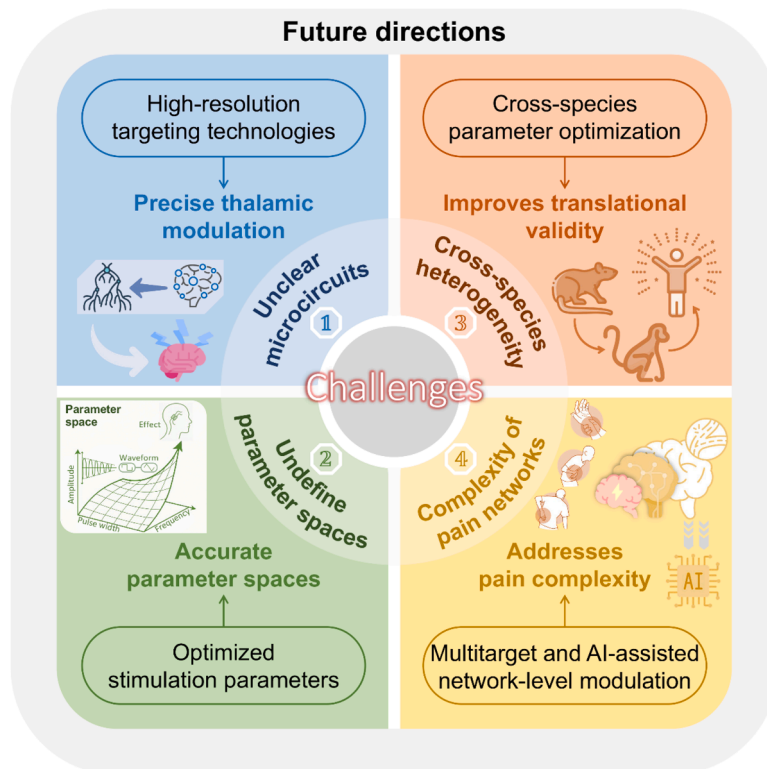


Fig. 3. Key challenges and future directions in precision thalamic-targeted pain neuromodulation.

Current approaches to thalamic-targeted neuromodulation for pain encounter several major obstacles: (1) poorly defined anatomical boundaries and overlapping microcircuits within thalamic nuclei, which hinder precise modulation of pain-related pathways; (2) undefined stimulation parameter space; (3) cross-species heterogeneity in thalamic structure and function; and (4) the complexity and individual variability of pain networks. To overcome these barriers, we propose a precision framework built on four pillars: high-fidelity targeting to resolve anatomical ambiguity, multi-dimensional optimization of frequency and waveform parameters, cross-species validation to improve translational predictability, and artificial intelligence (AI)-driven adaptive systems for personalized network-level modulation.

Furthermore, species-specific neurochemical profiles, including the distribution of key neurotransmitter receptors and neuromodulators [227,228], alter neuronal excitability and circuit dynamics to both disease states and exogenous stimulation, making the translation of stimulation parameters non-trivial. These differences collectively undermine the premise that a protocol effective in an animal model will engage a comparable neural substrate or produce a similar network effect in patients, contributing to variable clinical outcomes. These considerations highlight the necessity of a more systematic approach to account for interspecies divergence when translating preclinical neuromodulation findings.

- (4) *Complexity and variability of pain networks*: Chronic pain pathophysiology drives substantial thalamic reorganization, altering baseline neural activity and potentially recalibrating the circuit's responsiveness to exogenous stimulation. This inherent neuroplasticity is intertwined with the multidimensional nature of pain, encompassing sensory, emotional, and cognitive components, and is actively and dynamically modulated by psychosocial context. Critically, psychosocial factors such as pain catastrophizing, maladaptive beliefs, and social support do not merely correlate with pain but fundamentally reshape neural circuit dynamics, contributing to the profound inter-individual variability observed in both pain perception and treatment outcomes. Neuroimaging evidence mechanistically links these factors to specific network alterations: for instance, pain catastrophizing amplifies activity within attention- (e.g., dorsolateral PFC and ACC), emotion- (e.g., claustrum/amygdala circuitry), and anticipation-related regions (e.g., medial frontal cortex and cerebellum), thereby intensifying pain processing across thalamocortical and corticolimbic networks [229]. Similarly, social support has been shown to exert a regulatory influence on threat- and emotion-related circuits, including attenuating activity in key regions such as the hippocampus and thalamus, and modulating thalamo-cortical functional connectivity, thereby facilitating the long-term extinction of threat responses [230]. Moreover, the resulting fluctuations in clinical pain intensity are associated with distinct, state-dependent dysrhythmias in thalamocortical connectivity, such as the abnormal dynamic coupling between specific thalamic nuclei and sensory or default-mode cortical regions in chronic low back pain [139]. In essence, the pain network is not a static anatomical entity but a distributed, evolving functional system whose state is continuously shaped by the interaction between neuropathology and psychosocial context. This inherent complexity and variability, compounded by individual differences in neuroanatomy and psychological profile, constitute the core challenge for any standardized neuromodulation therapy.

Given this foundational understanding, the variable and often suboptimal clinical outcomes of neuromodulation for chronic pain become explicable. For instance, inconsistent responder rates in thalamic DBS trials are not solely a technical targeting issue but likely reflect the failure of a fixed stimulation paradigm to engage the dynamic and heterogeneous network pathology described above. Therefore, the therapeutic imperative shifts from static anatomical targeting to the development of precision neuromodulation strategies capable of adapting to an individual's unique and fluctuating neural state. Such strategies should account not only for neuroanatomical and neurophysiological individuality but also for the dynamic influence of psychosocial dimensions. While this represents a formidable challenge, pioneering work in related neurological disorders offers a conceptual roadmap. For example, adaptive DBS for Parkinson's disease, which uses patient-specific neural biomarkers (e.g., gamma band oscillations in the subthalamic nucleus or motor cortex) to adjust stimulation in real time, has demonstrated superior symptom control compared to continuous stimulation [231]. This proof-of-concept powerfully illustrates the feasibility and potential benefit of data-driven, closed-loop neuromodulation. However, its translation to chronic pain is non-trivial, as it requires identifying equally reliable and context-sensitive neural biomarkers for a condition defined by its multidimensionality and psychosocial modulation. Addressing this gap is the critical next step toward therapies that can contend with the true complexity of chronic pain networks.

In summary, neuromodulatory strategies targeting the thalamus for chronic pain encounter fundamental and interrelated challenges that span spatial, temporal, and conceptual dimensions. Spatially, limitations in anatomical targeting and parameter optimization persist. Temporally and biologically, these strategies must contend with the dynamic plasticity of pain networks and the translational complexities arising from cross-species differences. Most critically, at a conceptual level, they must evolve to incorporate a holistic understanding of pain, wherein psychosocial factors are not mere confounders but active modulators that fundamentally shape both the clinical pain experience and the underlying neural circuit dynamics targeted for intervention.

5.2. Future directions for precision neuromodulation

To advance thalamic-targeted neuromodulation for chronic pain, future work should focus on addressing the key challenges through four main pathways (Fig. 3). First, achieving anatomical precision demands high-resolution targeting technologies. The current resolution of neuromodulation methods is not sufficient to reliably distinguish between small, adjacent thalamic nuclei. Emerging technologies are enabling more refined targeting configurations for these structures [185,232]. For instance, the integration of directional DBS [233,234] with ultra-high field MRI guidance [235] allows for precise current steering toward specific thalamic subregions. Similarly, combining MRI-guided FUS [30,236] with real-time electrophysiological feedback in closed-loop systems [237], offer promising avenues for selective engagement of pain-related nuclei. Complementary innovations, such as pulse-width modulated TI [224] and dual-crossed ultrasonic stimulation [238], could further refine spatial specificity. Ultimately, integrating these advanced targeting configurations with fMRI-guided planning and dynamic connectivity analyses will be crucial for enhancing anatomical localization accuracy and achieving precision neuromodulation. Second, addressing the underdeveloped stimulation parameter space requires a fundamental shift from empirical frequency selection to a principled exploration of the multidimensional parameter space, encompassing not only frequency but also waveform, amplitude, and pulse width. A deeper biophysical understanding of how these parameters collectively influence neuronal excitability, synaptic transmission, and network resonance in thalamic circuits is essential. This demands systematic *in vitro* and preclinical *in vivo* studies to dissect how specific parameter configurations individually and

synergistically modulate neural dynamics and behavioral outcomes in different pain states. Computational biophysical models, calibrated with cross-species electrophysiological data and incorporating cell-type-specific properties, will be critical for predicting effective stimulation sets for distinct thalamic pathways. This mechanistic framework, supported by evidence of superior outcomes with composite parameter metrics in Parkinson's disease and depression DBS studies [213,225], aims to replace trial-and-error approaches with predictive, physiology-guided parameter selection.

Third, to mitigate the confounding effects of species differences, a rigorous translational framework is essential. This begins with identifying conserved circuit-level biomarkers by systematically aligning preclinical data, from *in-vitro* slice electrophysiology and *in-vivo* circuit dynamics in rodent models, with human data obtained through neuroimaging, intracranial recordings, and subjective pain reports. The cornerstone of this approach is the development of species-specific computational biophysical models. Informed by the cross-species datasets, these models simulate neuromodulation effects and predict optimal stimulation parameters for human trials based on preclinical findings. This model-guided strategy is further refined through iterative testing in non-human primates and early-phase clinical studies, thereby de-risking clinical translation and directly addressing the root of inconsistent therapeutic outcomes.

Fourth, addressing the combined challenge of network complexity and individual variability requires intelligent neuromodulation strategies capable of circuit-aware adaptation. Technologies with multifocal capabilities, such as TIS and FUS, can be employed to co-modulate key nodes within pain-processing networks. For example, simultaneous stimulation of the MD nucleus and its prefrontal or anterior cingulate cortical projections may disrupt maladaptive circuitry more effectively than single-site approaches. However, brain states are dynamic and heterogeneous, fixed open-loop stimulation often yields variable outcomes across time and individuals, and the vast amount of physiological data necessitates rapid extraction of informative features to support real-time decisions. Moreover, traditional closed-loop control typically based on threshold-triggered responses to a single electrophysiological biomarker, lacks the ability to interpret complex, high-dimensional neural states or to learn and adapt to individual-specific network dynamics. Such systems operate reactively rather than predictively and do not optimize stimulation parameters across multiple dimensions (e.g., frequency, amplitude, and target location) in a coordinated manner. Therefore, advancing toward artificial intelligence (AI)-driven adaptive closed-loop systems represents a necessary evolution beyond conventional closed-loop paradigms. These systems are essential because they can integrate and learn from multimodal neurophysiological data, including EEG features (e.g., gamma band power) [207,208,239], thalamocortical oscillations (e.g., theta-gamma coupling) [240], and fMRI-based connectivity [241], to define individualized neural fingerprints and infer latent brain states associated with symptom expression.

In practice, an AI-driven adaptive system could be implemented through a structured, personalized framework, as shown in recent translational work [242]. This framework includes: (1) a personalized monitoring phase, where individual baseline data (e.g., cognitive performance, anatomical measures like head circumference, and resting-state neurophysiology) are collected, often remotely, to establish a personal profile; (2) a stimulus exploration and model-building phase, where cloud-based algorithms, such as personalized Bayesian Optimization, use this profile to efficiently probe the stimulation parameter space. The goal is to build a personalized stimulus-response model that links specific stimulation parameters to changes in neural dynamics and behavioral or clinical outcomes. By accumulating data across users, such systems can refine protocols over time, optimizing outcomes for both the individual and future users with similar profiles; (3) an adaptive treatment phase, in which the system, informed by the continuously updated model and real-time (or frequent) performance/physiological feedback, selects and delivers personalized stimulation parameters aimed at steering brain network activity toward a target, healthier dynamical regime for sustained benefit. This data-driven, closed-loop, individualized approach, validated in cognitive enhancement studies, holds promise for scalable precision neuromodulation in chronic pain therapy.

However, realizing this strategy in clinical practice requires addressing critical translational challenges. Technically, the robustness and generalizability of algorithms are paramount. Models must effectively manage noise and non-stationarities inherent in real-world neural data and perform reliably across heterogeneous patient populations to accommodate the inevitable clinical diversity. This facilitates a shift from reactive, biomarker-triggered stimulation to proactive, model-predictive neuromodulation. Such systems enable real-time, context-sensitive adjustment of stimulation parameters, aiming not only to suppress pathological biomarkers but also to restore adaptive network dynamics and promote sustained symptom relief. This establishes a dynamic, personalized therapeutic approach that evolves with the patient's fluctuating brain state. Equally important are the ethical and practical considerations for clinical deployment. These include safeguarding data privacy and security, given the highly sensitive nature of neural data, ensuring algorithmic transparency and interpretability to foster clinician trust, enable accountability for treatment decisions, and meet potential regulatory standards; and, crucially, preserving patient autonomy and informed consent, ensuring that patients remain central to understanding and controlling their personalized therapy. By integrating multifocal co-modulation with AI-driven adaptation while proactively addressing these challenges, we can advance beyond static or conventional closed-loop stimulation paradigms toward context-aware, and self-optimizing neuromodulation tailored to individual pathophysiology.

To fully realize the thalamus's potential in pain modulation, future work must converge on four priority areas: (1) advancing high-resolution targeting to overcome anatomical ambiguity, (2) establishing a multidimensional parameter framework for circuit-specific engagement, (3) bridging the translational gaps with cross-species validation, and (4) pioneering network-level personalization with AI-driven adaptive systems (Fig. 3). Implementing this precision medicine approach demands sustained interdisciplinary collaboration. Success hinges on translating mechanistic insights into clinical applications while addressing the interplay between neuromodulation's biophysical effects, neurophysiological mechanisms, and the psychosocial dimensions of chronic pain.

5.3. Potential side effects and adverse events of thalamic-targeted neuromodulation

While thalamic neuromodulation offers therapeutic potential for chronic pain, its clinical translation necessitates thorough

assessment of side effects. The thalamus is a functionally heterogeneous structure with extensive cortical and subcortical connections that regulate sensorimotor, cognitive, and affective functions. Thalamic-targeted neuromodulation (e.g., DBS, TIS, and FUS) may inadvertently affect adjacent nuclei or white matter tracts through current spread, resulting in unintended neurological and behavioral consequences. Clinical reports indicate that side effects depend on the targeted thalamic subregion [243,244]. Commonly reported adverse events include paresthesias (often associated with the VP nuclei), ataxia (linked to cerebellothalamic pathways), and dysarthria. Alterations in cognition, mood, or arousal, though less frequent, reflect the integral role of the thalamus within limbic and associative circuits. These effects arise from anatomical and electrophysiological factors. Off-target modulation often results from current diffusion into adjacent structures, for example, spread to the internal capsule may induce motor effects [245], while involvement of limbic nuclei can influence emotional processing [246,247]. Suboptimal stimulation parameters, such as excessive amplitude or frequency, may exacerbate side effects by recruiting larger neural populations or disrupting physiological oscillations [222].

Therefore, mitigation strategies are essential and align with the pursuit of precision neuromodulation. First, advanced targeting techniques, such as high-resolution structural imaging, patient-specific tractography, and intraoperative electrophysiological mapping can enhance spatial specificity and minimize off-target stimulation. Second, adaptive closed-loop systems (as discussed in Section 5.2) hold considerable promise for dynamically adjusting stimulation parameters within a therapeutic window, thereby maintaining efficacy while reducing side effects. Finally, the implementation of comprehensive preoperative planning and postoperative monitoring protocols is critical for the early detection and management of adverse events. Proactively addressing these safety considerations is fundamental to the development of clinically viable, well-tolerated thalamic neuromodulation therapies for chronic pain.

6. Conclusion

Recent research has progressively refined our understanding of thalamic function in pain, moving beyond a simplified relay model to reveal a complex integrator of sensory and affective information. The MITN have emerged as critical hubs in the distributed network that shapes the chronic pain experience. This refined perspective complements rather than replaces traditional anatomical frameworks by emphasizing dynamic circuit interactions alongside established functional organizations. Concurrently, technological advances in neuromodulation have created unprecedented opportunities for intervention. Progress in four key areas is particularly promising: high-resolution targeting methods are enabling precise engagement of specific thalamic subregions; cross-species parameter optimization frameworks help bridge translational gaps; multi-node network modulation strategies address distributed pain pathways; and AI-driven adaptive systems facilitate personalized therapy. The convergence of these approaches forms an integrated precision neuromodulation framework that moves beyond conventional strategies. By aligning technological innovation with circuit-level mechanistic insights, this emerging paradigm offers a promising path toward more effective and individualized management of chronic pain, potentially improving functional outcomes and quality of life for affected individuals. To fully realize this potential for chronic pain management, future research must address a crucial question: how distinct cell types (e.g., excitatory thalamocortical neurons versus local inhibitory interneurons) within thalamic circuits differentially maintain the chronic pain state and respond to neuromodulation. Understanding these mechanisms will be essential for refining thalamic targeting and stimulation parameters, thereby translating our mechanistic framework into more effective and durable therapies for individuals suffering from chronic pain.

Authors' contribution

Conceptualization: Z.J.L. and L.H. Writing—original draft: Z.J.L., J.R. and X.J.L. Writing—review & editing: Z.J.L., X.J.L., and L.H. Visualization: Z.J.L. and F.R.Z. Funding acquisition: X.J.L. and L.H. Project administration: L.H. Supervision: L.H.

Ethics approval

Not applicable.

Data availability

Not applicable.

Declaration of competing interest

The views expressed in this article are those of the authors. The funders had no role in the conduct of the study, article preparation, or the decision to submit for publication. The authors declare no conflict of interest.

Acknowledgments

L.H. is supported by the National Key Research and Development Program of China (2024YFC3607600) and Beijing Natural Science Foundation (L246074). X.J.L. is supported by the National Natural Science Foundation of China (32171077) and a grant from the Youth Innovation Promotion Association, CAS.

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