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Non-Invasive Brain Stimulation in Chronic Pain: Current Evidence, Network Perspectives and Paths to Personalization

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ABSTRACT

Chronic pain is increasingly conceptualized as a network-level neuroplasticity disorder involving maladaptive interactions among sensory, affective-salience, and descending modulatory pathways. This narrative review synthesizes evidence for non-invasive brain stimulation (NIBS) in chronic pain—transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), and low-intensity transcranial focused ultrasound (LITUS)—and outlines systems neuroscience-grounded routes to personalization. High-frequency motor cortex rTMS shows the most consistent, though modest, short-term analgesic effects, especially in neuropathic pain and fibromyalgia, and currently has the strongest guideline support. tES, particularly tDCS, produces small, heterogeneous benefits with low-certainty evidence, whereas tACS and tRNS remain largely experimental. LITUS provides millimeter-scale focality and access to deep pain-relevant structures, with early preclinical and human studies suggesting promising but preliminary analgesic effects. Across modalities, responses are highly variable and usually short-lived, reflecting reliance on population-derived targets and protocol-based dosing that disregard individual network organization. We highlight emerging strategies for target and parameter personalization, including graph-theoretical targeting, individualized electric/acoustic field modeling, and closed-loop neuromodulation guided by electrophysiological and imaging biomarkers, to enable more mechanism- and network-informed, phenotype-sensitive NIBS for chronic pain.

1 | Introduction

Chronic pain, commonly defined as pain lasting longer than 3 months, is a leading cause of disability worldwide, affecting an estimated 1.9 billion people [1]. It is associated with substantial functional impairment and economic burden [2, 3]. Limited effectiveness of standard treatments, together with decades of opioid overprescribing, has contributed to the opioid epidemic in the United States [4]. Although care has shifted toward multimodal, biopsychosocial frameworks prioritizing non-pharmacological and other non-opioid approaches, responses remain highly variable and often inadequate, underscoring the need for safer, more effective, and ultimately more personalized therapies.

Clinically, chronic pain is often categorized as nociceptive, neuropathic, or nociplastic [5]. Nociceptive pain arises from activation of peripheral nociceptors by tissue injury; neuropathic pain from a lesion or disease of the somatosensory system; and nociplastic pain from altered nociception, with central

Key Points

- Chronic pain can be framed as an enduring imbalance in distributed brain systems that encode nociceptive input, assign salience and affective value, and regulate descending control.
- Current evidence for non-invasive brain stimulation (NIBS) shows modest, typically short-lived analgesic effects with substantial inter-individual variability, highlighting the limits of protocol-based dosing and population-derived targets.
- Target personalization aims to move stimulation from group-average sites to individual network "entry points," for example using connectomic and graph-theoretical approaches to improve circuit relevance.
- Achieving more durable and clinically meaningful effects will likely require integrating personalized targeting (*where* stimulation is delivered) with individualized, field- and biomarker-informed dosing (*how* and *when* stimulation is delivered), including emerging closed-loop approaches.

(and often peripheral) sensitization and disturbed pain modulation in the absence of a clear structural lesion [6–8]. In practice, these mechanisms frequently co-occur [9]. Converging evidence indicates that chronic pain is sustained by network-level neuroplastic changes, involving maladaptive interactions among partially dissociable circuits that consolidate nociplastic mechanisms, weaken descending inhibitory control, reshape oscillatory dynamics, and bias valuation toward pain-related signals [10–13].

Within this landscape, neuromodulation seeks to directly engage pain-related circuits. Historically, invasive approaches centered on deep brain stimulation (DBS) of putative "pain centers" in thalamic relays, brainstem nuclei, and later cortical targets for otherwise refractory pain, with variable clinical benefit and largely empirical target selection [11]. Although optimized DBS protocols continue to yield encouraging results [14, 15], attention has increasingly shifted toward non-invasive tools that are more broadly deployable and generally considered safer [16]. Neuromodulation strategies broadly span brain stimulation, spinal cord stimulation (SCS), and peripheral nerve stimulation (PNS) [17, 18]. SCS and PNS are established treatments for selected pain conditions but fall outside the scope of this article and have been reviewed elsewhere (e.g., [19, 20]). Here we focus on non-invasive brain stimulation (NIBS) as a means to (transcranially) modulate distributed pain networks and as a testbed for network-informed, personalized neuromodulation strategies.

We first outline the systems-level foundations of chronic pain, then review key NIBS modalities, including transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), and low-intensity transcranial focused ultrasound (LITUS). Finally, we discuss emerging approaches to target and dose personalization, including individualized connectomic and graph-theoretical targeting, parameter personalization, and closed-loop neuromodulation.

1.1 | Network Imbalance in Chronic Pain

Chronic pain is conceptualized as a systems-level neuroplasticity disorder, with several theoretical models proposing that it is sustained by an imbalance across three partially overlapping pathways: (i) a lateral sensory-discriminative pathway that encodes the physical features of pain (location, intensity, quality); (ii) a medial affective-salience pathway that assigns threat value, affective load, and attentional priority; and (iii) a descending modulatory pathway that normally exerts top–down inhibitory control over nociceptive transmission (Figure 1) [10, 21–24]. When lateral and medial drive chronically exceed descending control, pain becomes persistent, effectively amplified, and functionally disabling [10]. Resting-state neuroimaging studies demonstrate aberrant coupling between pain-related regions and multiple large brain networks. Most prominently, the default mode network (DMN; medial prefrontal cortex, mPFC; posterior cingulate cortex, PCC; precuneus; inferior parietal lobule, IPL; medial temporal lobe, MTL), salience/attention networks (including anterior insula and anterior cingulate cortex, ACC), and executive control networks (including the dorsolateral prefrontal cortex, dlPFC, and the posterior parietal cortex, PPC), supporting a multi-network account of chronic pain [10, 25–28]. Such a network-level framing aligns with earlier distributed accounts of pain. Melzack's Neuromatrix (or "pain matrix") formalized the view that pain emerges from patterned activity across an interconnected network spanning somatosensory, limbic, and thalamocortical systems, supporting sensory-discriminative, affective-motivational, and cognitive-evaluative components of the experience [21, 22]. From a computational perspective, predictive processing frames pain as an inference about bodily threat that integrates nociceptive/interoceptive input with prior expectations and context; chronic pain may emerge when threat priors are overweighted, leading ambiguous signals to be repeatedly interpreted as pain even after peripheral drivers subside [29, 30]. Together, these accounts converge on chronic pain as an interaction among sensory, affective, and control systems consistent with the present systems-level framework.

The lateral sensory-discriminative pathway carries nociceptive information from dorsal root ganglia (DRG) via lamina I/V dorsal horn neurons into the spinal anterolateral system (spinothalamic tract), which ascends to lateral thalamic nuclei (VPL/VPM and posterior ventral nuclei such as VPI/VMpo) [10, 31, 32]. Activity further extends to primary and secondary somatosensory cortex (S1/S2), parietal operculum and posterior insula, first encoding pain location, intensity, and quality [10, 33, 34]. Adjacent M1 and supplementary motor areas are somatotopically organized and support sensorimotor integration [35, 36]. Chronic pain has been associated with thalamocortical dysrhythmia (e.g., abnormal low-frequency activity, disrupted synchrony) and somatotopic reorganization of thalamocortical nociceptive representations [37, 38].

Yet, whether the pain signal becomes associated with "suffering" depends largely on a parallel but distinct ascending route: the medial affective-salience pathway. Nociceptive signals ascend via spinoreticulothalamic and spinoparabrachial pathways through brainstem reticular formation/parabrachial

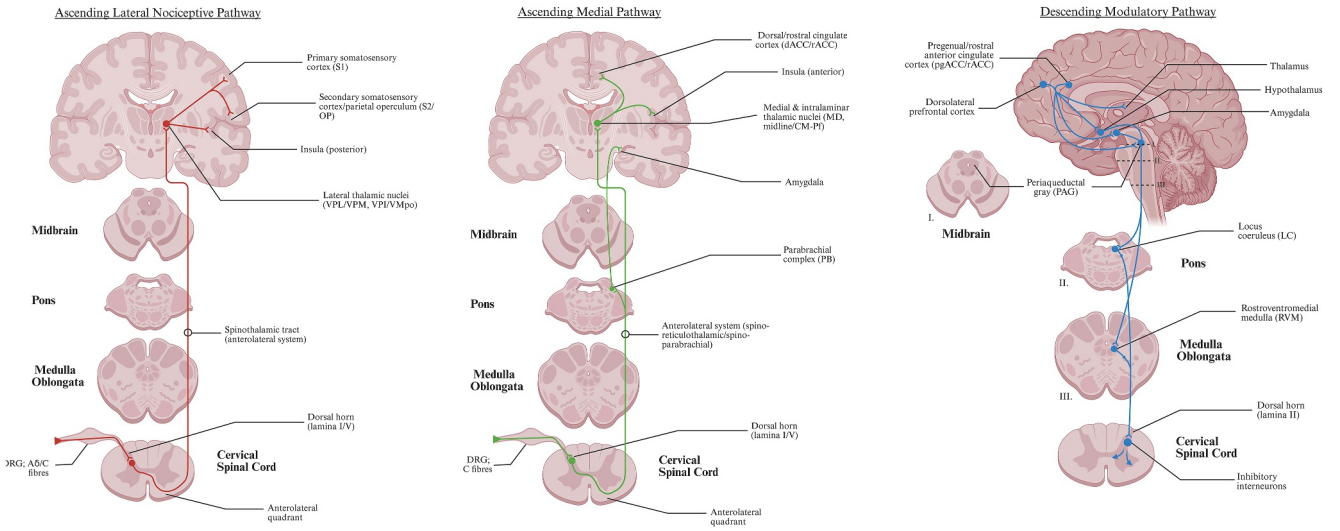

FIGURE 1 | Three partially dissociable pain pathways supporting sensory-discriminative, affective-salience, and descending modulatory processing. (a) Left: Ascending lateral pathway (red). Nociceptive Aδ (A-delta) and C primary afferents from dorsal root ganglia (DRG) terminate on projection neurons in the dorsal horn (lamina I/V) of the cervical spinal cord. Axons decussate and ascend in the contralateral anterolateral quadrant as the spinothalamic tract, synapsing in lateral thalamic nuclei, including the ventral posterior lateral (VPL) and ventral posterior medial (VPM) nuclei and posterior ventral nuclei such as the ventral posterior inferior (VPI) and ventral medial posterior (VMpo) nuclei. Thalamocortical projections relay to the primary somatosensory cortex (S1), secondary somatosensory cortex/parietal operculum (S2/OP), and posterior insula, encoding pain location, intensity, and quality. (b) Middle: Ascending medial pathway (green). Predominantly C-fiber input from the DRG activates lamina I/V dorsal horn neurons whose axons ascend in the anterolateral system via spinoreticulothalamic and spinoparabrachial projections. Spinoreticulothalamic fibers terminate in medial and intralaminar thalamic nuclei, including the mediodorsal (MD) nucleus and centromedian-parafascicular (CM-Pf) complex. Spinoparabrachial projections synapse in the parabrachial complex (PB) and project directly to the amygdala. Medial thalamic output targets dorsal/rostral anterior cingulate cortex (dACC/rACC) and anterior insula and engages multiple limbic regions, supporting attention and salience attribution, affective load, and aversive learning. (c) Right: Descending modulatory pathway (blue). Prefrontal and cingulate regions, including dorsolateral prefrontal cortex (dlPFC) and pregenual/rostral anterior cingulate cortex (pgACC/rACC), send projections to thalamic, hypothalamic, and amygdalar relays, as well as to the periaqueductal gray (PAG) in the midbrain. From the PAG, projections descend to brainstem monoaminergic nuclei, including the locus coeruleus (LC) in the pons and rostroventromedial medulla (RVM; including nucleus raphe magnus and adjacent reticular nuclei) in the medulla oblongata. LC and RVM neurons send fibers in the dorsolateral funiculus to the spinal dorsal horn (lamina II), where they modulate nociceptive transmission via inhibitory interneurons, providing top–down facilitation or suppression of ascending nociceptive signals.

complex to medial and intralaminar thalamic nuclei (e.g., MD, midline/CM-Pf), which project to rostral-dorsal ACC and anterior insula and interact with mPFC and limbic-striatal regions, including amygdala and ventral striatum [39–43]. Hence, this pathway overlaps strongly with salience and attentional control networks. Evidence from cingulate lesion studies shows that disrupting ACC reduces suffering and distress without abolishing nociceptive detection, whereas dACC activity scales with ratings of subjective unpleasantness across modalities [44–46]. With persistent pain, strengthened S1 and DMN connectivity may contribute to the embodiment and chronification of pain, whereas longitudinal work shows that nucleus accumbens-mPFC coupling predicts transition from subacute to chronic pain, consistent with maladaptive valuation processes [10, 24, 47, 48]. Support vector machines trained on resting-state EEG from chronic neuropathic pain, tinnitus, Parkinson's, and depression, correctly distinguished chronic pain from controls with a ~93% accuracy rate and identified chronic pain-specific theta-beta/gamma abnormalities in sensorimotor regions, supporting a transdiagnostic network signature [38].

The third descending modulatory pathway regulates the two ascending streams and is responsible for context-dependent pain perception [49, 50]. Prefrontal and cingulate regions, including dlPFC, pregenual and rostral anterior cingulate cortex (pgACC/rACC), project through midline and brainstem structures such as the reticular nucleus of the thalamus, hypothalamus, periaqueductal gray (PAG), and rostroventromedial medulla (RVM) to the spinal cord [10, 51]. This cortico-brainstem-spinal axis can inhibit or, under some conditions, facilitate nociceptive transmission before it reaches full conscious elaboration [10, 52]. Neurochemically, it relies on monoamine (e.g., noradrenaline from locus coeruleus) and opioid mechanisms to gate nociceptive throughput [49, 53, 54]. Evidence from Neurosynth meta-analyses and functional imaging of chronic pain cohorts frequently shows persistent engagement of lateral-medial pathway-related regions, together with altered and often ineffective recruitment of the descending modulatory pathway, supporting the idea that chronification may reflect failure of endogenous suppression [24].

The ascending lateral, medial, and descending pathways are dissociable yet work in coordination. Simply put, persistent thalamocortical hyperexcitability in the lateral stream sustains afferent gain, cingulo-insular salience networks in the medial stream assign persistent distress, and prefrontal-brainstem descending control fails to suppress the signal. Thus, chronic pain is increasingly viewed as a breakdown in the coordinated

functioning of sensory, affective, and control networks. Over time, this imbalance becomes reinforced through maladaptive neuroplasticity. NIBS aims to reverse these changes non-invasively: dampening hyperactive sensory-discriminative coding, decoupling pain from pathological salience and catastrophising, and re-engaging top–down inhibitory control.

2 | Methodology: Literature Search and Evidence Synthesis

This article is a narrative review intended to integrate mechanistic and clinical evidence on non-invasive brain stimulation (NIBS) for chronic pain within a network neuroscience framework and to outline practical routes toward personalization. The literature was identified through structured searches of PubMed and Google Scholar, supplemented by targeted searches for key modalities and pain syndromes, and by backward and forward citation tracking of relevant systematic reviews, meta-analyses, clinical guidelines, and landmark experimental studies. Searches primarily covered the period from January 2010 to January 2026 (including selected landmark papers) and used combinations of terms relating to chronic pain and NIBS modalities (e.g.,: "chronic pain," "neuropathic pain," "fibromyalgia," with "repetitive transcranial magnetic stimulation/rTMS," "theta burst," "tDCS," "tACS," "tRNS," "transcranial electrical stimulation," "low-intensity focused ultrasound/tFUS," "neuromodulation," "EEG," "personalization").

Evidence was synthesized qualitatively, prioritizing randomized, sham-controlled trials and meta-analytic summaries where available. Evidence certainty was drawn primarily from published systematic reviews, meta-analyses, and guideline assessments; where these were lacking (especially for emerging modalities), certainty was judged using consistent criteria: study design, risk of bias (blinding/sham adequacy, allocation concealment), sample size/precision, consistency/heterogeneity, and indirectness (population, target, and parameter differences). Mechanistic and network-level claims were emphasized only when supported by neuroimaging, electrophysiology, and causal perturbation evidence; otherwise, they were presented as hypotheses.

3 | NIBS Techniques for Chronic Pain: Current Evidence

3.1 | TMS

Transcranial magnetic stimulation (TMS) operates by driving brief, high-intensity currents through an electromagnetic coil to generate a rapidly changing magnetic field, which penetrates the scalp and induces secondary electrical currents that modulate neuronal excitability in underlying brain regions [55]. Clinically, TMS is often delivered as trains of pulses (repetitive TMS; rTMS), including patterned protocols such as intermittent theta-burst stimulation (iTBS), and its effects are shaped by key stimulation parameters, including coil type/orientation, anatomical target, stimulation frequency, and dose [19]. Converging experimental data indicate that rTMS produces multi-level neuroplastic adaptations in pain-modulatory circuits (including glutamatergic, monoaminergic, and neurotrophin-mediated mechanisms) [16, 56]. Most commonly, rTMS targets M1 in chronic pain, which is thought to engage opioidergic mechanisms and recruit descending pathway nodes (e.g., PAG-RVM), supporting top–down control of nociceptive processing [57, 58]. Moreover, M1 stimulation is thought to recruit dissociable, layer-specific output pathways, with layer-5 projections engaging subcortical antinociceptive circuits (including PAG-related routes) to reduce sensory hypersensitivity and layer-6 projections acting via mediodorsal thalamus–nucleus accumbens circuitry to attenuate the aversive–affective dimension of neuropathic pain [59]. Analgesic protocols most frequently employ high-frequency (10–20 Hz) stimulation at 80%–120% resting motor threshold (RMT), delivering approximately 1000–2000 pulses per session over 5–10 sessions [60]. dlPFC is also commonly targeted with a similar rationale as to M1 (e.g., recruitment of descending pathway nodes) [61] (Figure 2; Table 1).

A 2018 meta-analysis (27 trials; $n = 655$) found a small short-term analgesic effect of rTMS versus sham across chronic pain conditions (SMD −0.22; 95% CI −0.29 to −0.16), with low-quality evidence and risk of bias; effects were driven primarily by high-frequency (≥ 5 Hz) stimulation of M1 in single-dose studies [62]. A more recent meta-analysis (38 studies) reported a moderate short-term effect in neuropathic pain (pooled SMD −0.66; 95% CI −0.87 to −0.46), particularly for high-frequency, especially 10 Hz, excitatory M1 stimulation, with signals for sustained benefit up to ≥ 2 months and no excess adverse events, though substantial heterogeneity and protocol variability [63]. Moreover, a systematic review of seven RCTs ($n = 217$) found that 10-Hz rTMS in fibromyalgia significantly reduced pain (SMD −0.72; 95% CI −1.12 to −0.33) and improved quality of life, but not depression, with no significant difference between M1 and dlPFC stimulation sites [64].

In line with these findings, European expert guidelines only assign "definite efficacy" to high-frequency M1 rTMS for neuropathic pain and probable efficacy for high-frequency left M1 or dlPFC stimulation in fibromyalgia [65], and with updated NeuPSIG recommendations identifying high-frequency rTMS to M1 as the only consistently supported non-invasive neuromodulation option for refractory neuropathic pain, recommended as a third-line adjunctive treatment given limited evidence certainty and low treatment availability [66].

Despite guideline-level recommendations, rTMS evidence in chronic pain is still limited by underpowered trials, substantial protocol heterogeneity (target, frequency/intensity, dosing/maintenance, sham/blinding), pooled heterogeneous pain phenotypes, and typically short follow-up, producing limited, low-certainty conclusions. Larger preregistered multicentre RCTs with harmonized outcomes/reporting, mechanism-informed stratification, and personalization with dose/maintenance optimization are needed.

3.2 | tES

Transcranial electrical stimulation (tES) uses low-intensity currents applied via scalp electrodes to modulate subthreshold

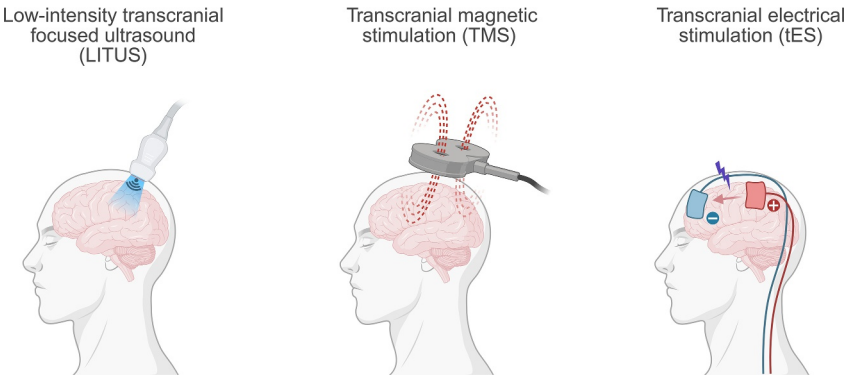

FIGURE 2 | Overview of non-invasive brain stimulation modalities for chronic pain. Schematic comparison of three non-invasive neuromodulation modalities: low-intensity transcranial focused ultrasound (LITUS; left), transcranial magnetic stimulation (TMS; middle), and transcranial electrical stimulation (tES; right). See Table 1 for an overview of commonly used modality-specific stimulation targets and parameters. ACC = anterior cingulate cortex; dlPFC/DLPFC = dorsolateral prefrontal cortex; M1 = primary motor cortex; PAG = periaqueductal gray; S1 = primary somatosensory cortex; tACS = transcranial alternating current stimulation; tDCS = transcranial direct current stimulation; VPL = ventral posterolateral nucleus of the thalamus.

membrane potentials, alter large-scale network excitability, and, in oscillatory modes, shape ongoing neural rhythms within pain-related circuits [67]. Its clinical effects are shaped by current type (e.g., direct, alternating, or random noise), montage, polarity, intensity and stimulation site, with generally broader, less focal fields than TMS [16, 68]. Primary cortical targets across tES methods strongly overlap with those for rTMS (i.e., M1 and dlPFC) (Figure 2; Table 1).

Transcranial direct current stimulation (tDCS) delivers a weak constant current (typically 0.5–2 mA) that shifts cortical excitability (anodal depolarizing, cathodal hyperpolarising) and modulates plasticity within thalamo-cortico-limbic pain networks; its effects are cumulative, so repeated sessions are usually required for clinically meaningful benefit [19, 69]. A meta-analysis (27 RCTs; n = 747) reported a modest short-term (0–1 week) reduction in pain intensity across heterogeneous chronic pain conditions (SMD −0.43; 95% CI −0.63 to −0.22), based on very low quality evidence [62]. A more recent umbrella review of 41 systematic reviews and meta-analyses (n = 18,018) suggests that tDCS may be beneficial in selected conditions such as fibromyalgia, migraine and neuropathic pain, but the underlying studies are generally low quality, and overall certainty remains low [70]. tDCS has few side effects, is approved for pain in Europe, and has received a weak positive recommendation for M1 stimulation in neuropathic pain, with inconclusive expert panel recommendations for spinal cord injury pain and fibromyalgia, including a level A recommendation *against* M1 tDCS for chronic lower back pain [19, 71, 72].

Transcranial alternating current stimulation (tACS) uses sinusoidal currents to entrain or disrupt aberrant oscillatory activity implicated in chronic pain (e.g., alpha) [73, 74]. Despite strong theoretical appeal, a recent systematic review [75] identified only four small trials: no significant effects in fibromyalgia [76], transient benefit in migraine targeting the occipital cortex [77], and mixed findings in low back pain, with one RCT reporting significant analgesia [78] and another no meaningful effect [79], resulting in no robust pooled effect and the conclusion that current evidence is insufficient to support clinical use in chronic pain. However, a recent randomized, double-blind, sham-controlled home-based tES trial (15 self-administered sessions; n = 120) found that both tDCS (2 mA, 20 min; left M1) and tACS (1 mA, 10 Hz, 20 min; bilateral frontal/prefrontal stimulation) reduced daily-reported pain intensity and several related symptoms versus sham, supporting the potential effectiveness of tES in remotely delivered protocols, although the sample over-represented primary pain, which may limit generalizability [80].

Another tES method, transcranial random noise stimulation (tRNS), delivers broadband alternating currents (0.1–640 Hz) to enhance cortical excitability via stochastic resonance, but chronic pain data are inconsistent and restricted to small studies with partially promising (e.g., fibromyalgia, multiple sclerosis), yet non-generalizable findings, so it should currently be regarded as an experimental modality pending adequately powered, protocol-optimized trials [69, 81, 82].

Across tDCS, tACS, and tRNS, mixed clinical efficacy despite plausible mechanisms may reflect inconsistent target engagement under standardized protocols [83]. At typical intensities, induced electric fields are weak and relatively diffuse, so intended generators may not be modulated reliably across individuals; for tACS, this is further limited when stimulation frequency mismatches an individual's peak rhythm, rhythms drift over time, or stimulation occurs in states less conducive to entrainment (e.g., high cognitive load) [75, 84, 85]. For tRNS, effects appear strongly parameter- and dose-dependent, with nonlinear intensity–response relationships, sensitivity to frequency band/bandwidth, and indications that longer or repeated dosing may be required for durable plasticity [86, 87]. These challenges are amplified when trials pool heterogeneous pain phenotypes, potentially diluting effects restricted to specific network dysfunctions and motivating personalized, target- and parameter-optimized tES approaches.

Finally, an emerging tES technique is transcranial temporal interference stimulation (tTIS). tTIS applies two scalp-delivered kHz sinusoids with a small frequency offset so their superposition forms an amplitude-modulated field whose low-

TABLE 1 | Comparison of non-invasive brain stimulation modalities for chronic pain.

Modality	Mechanistic emphasis and typical targets	Typical protocol parameters in chronic pain	Pain subtypes/ conditions with most support	Evidence level	Key gaps for clinical translation
TMS (rTMS/ iTBS)	Induces focal cortical currents; engages distributed pain-modulatory circuits. Most commonly targets contralateral M1; dlPFC also used.	High-frequency rTMS 10–20 Hz at 80%–120% RMT; ~1000–2000 pulses/ session over ~5–10 sessions (typical).	Neuropathic pain (contralateral M1). Limited support/ probable efficacy (HF left M1/dlPFC) in fibromyalgia.	Best-supported modality; guideline-level endorsement strongest for neuropathic pain (high-frequency M1 rTMS). Effects typically small-to-moderate and often short-lived.	Heterogeneous protocols/outcomes and suboptimal sham/blinding; underpowered trials with short follow-up; unclear optimal dose, spacing, and maintenance; need multicenter head-to-head trials (personalized vs. standard; E-field normalization vs. %RMT) with biomarker-based phenotyping and target-engagement measures.
tDCS (tES)	Subthreshold modulation of membrane potentials and plasticity; broad fields. Targets overlap with TMS (M1; contralateral, dlPFC; bilateral).	0.5–2 mA for ~20 min; repeated sessions usually required.	Selected conditions (e.g., fibromyalgia, migraine, neuropathic pain). Evidence negative/inconclusive in chronic low back pain depending on protocol.	Low/very low certainty overall; weak positive recommendation for M1 tDCS in neuropathic pain in some guidelines; several conditions remain inconclusive.	Optimizing montage/ dose; controlling placebo/nocebo; linking electric-field dosing to target engagement; adequately powered, placebo/nocebo controlled, condition-specific trials: Standard versus personalized procedure comparisons
tACS (tES)	Sinusoidal currents intended to entrain or disrupt pain-relevant oscillations (e.g., alpha); commonly targets occipital cortex (migraine) or frontal/ motor sites.	Typically, ~0.4–1 mA for ~20 min at fixed frequencies; emerging work aligns frequency to individual peak rhythms (e.g., alpha, theta) and explores closed-loop delivery.	Preliminary/mixed findings (e.g., migraine, low back pain); null findings reported in fibromyalgia.	Insufficient for clinical recommendation; mechanistic rationale stronger than current clinical evidence.	Variable entrainment/ target engagement; frequency mismatch to intrinsic rhythms; state dependence; heterogeneous phenotypes dilute effects; need parameter and phenotype personalization; test closed-loop and EEG-gated designs
tRNS (tES)	Broadband noise intended to boost excitability via stochastic resonance; often applied to M1 or dlPFC.	Broadband (0.1–640 Hz); intensity usually 1–2 mA; sessions and dosing schedules vary.	Small studies with inconsistent signals (e.g., fibromyalgia, multiple sclerosis-related pain).	Experimental; evidence base small and heterogeneous.	Uncertainty about optimal bandwidth/ intensity and dose–response; nonlinear effects; longer/repeated dosing may be required for durable

(Continues)

TABLE 1 | (Continued)

Modality	Mechanistic emphasis and typical targets	Typical protocol parameters in chronic pain	Pain subtypes/ conditions with most support	Evidence level	Key gaps for clinical translation
					plasticity; inter-individual electric-field variability; need protocol standardization and adequately powered RCTs.
tTIS (tES)	Depth-capable envelope modulation using 2 kHz currents; theoretical access to deep pain-relevant nodes (e.g., thalamus/ ACC/striatal circuits) via scalp electrodes.	Not established in chronic pain; key variables include carrier frequencies, Δf envelope, montage, intensity, and session structure.	None established.	No clinical efficacy evidence in chronic pain to date; experimental/early feasibility only.	Validate target engagement and quantify off-target cortical stimulation, establish safety and credible sham/ blinding, and optimize montage and carrier/Δf parameters; patient RCTs.
LITUS (tFUS)	Pulsed acoustic energy mechanically perturbs membranes and modulates excitability with high spatial precision; can access deep targets (e.g., ACC, thalamus/ VPL, insula, M1/ S1, PAG).	Single 20–40 min sessions or repeated brief sonications within a visit; duty cycle ~5%–50% (target-dependent). Fundamental frequency typically ~0.5–0.65 MHz; ISPTA ~0.15–1.6 W/ cm^2; ISPPA ~3.5–132 W/cm^2; MI ~0.20–1.20	Encouraging early signals in experimental and small chronic pain studies (e.g., ACC-targeted protocols).	Promising but early-stage; clinical evidence limited by small samples and protocol heterogeneity.	Skull-induced beam distortion and between-subject variability; need targeting verification (e.g., MR-ARFI/ fMRI); lack of standardized dosing and reporting (e.g., ITRUSST); larger sham-controlled trials.

Note: Evidence labels are qualitative summaries based on the cited systematic reviews/meta-analyses and guideline statements discussed in the manuscript. Protocol ranges are typical values reported in the chronic pain literature and vary by condition, target, and device; "evidence level" reflects the overall strength/consistency of available clinical data and guideline syntheses rather than a formal GRADE rating.
Abbreviations: ACC = anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, fMRI = functional magnetic resonance imaging, Hz = hertz, ISPPA = spatial-peak pulse-average intensity, ISPTA = spatial-peak temporal-average intensity, iTBS = intermittent theta-burst stimulation, ITRUSST = International Transcranial Ultrasound Stimulation Safety and Standardization (reporting) recommendations, kHz = kilohertz, LITUS = low-intensity transcranial focused ultrasound, M1 = primary motor cortex, mA = milliampere, mHz = megahertz, MI = mechanical index, min = minute(s), MR-ARFI = magnetic resonance acoustic radiation force imaging, PAG = periaqueductal gray, RCT = randomized controlled trial, RMT = resting motor threshold, rTMS = repetitive transcranial magnetic stimulation, S1 = primary somatosensory cortex, tACS = transcranial alternating current stimulation, tDCS = transcranial direct current stimulation, tES = transcranial electrical stimulation, tFUS = transcranial focused ultrasound, TMS = transcranial magnetic stimulation, tRNS = transcranial random noise stimulation, tTIS = transcranial temporal inference stimulation, VPL = ventral posterolateral thalamic nucleus, W/cm^2 = watts per square centimeter.
Sources: O'Connell et al. [62], Chang et al. [75], Xu et al. [94], Zhang et al. [97], Zhang et al. [144], Martin et al. [150] (ITRUSST), Ivanov et al. [151].

frequency envelope (Δf) can be "read out" by neuronal non-linearities, thereby modulating activity preferentially where the envelope is maximal [88, 89]. To our knowledge, tTIS has not yet been systematically tested in chronic pain (aside from one pending postherpetic neuralgia trial; *ChiCTR2500095096*). However, it is one of the few depth-capable NIBS techniques and therefore holds promise for expanding the reachable target set in chronic pain.

3.3 | LITUS

A depth-capable technique which has received significantly more attention is low-intensity transcranial focused ultrasound (LITUS). It delivers pulsed acoustic energy through the skull, mechanically perturbing neuronal membranes and modulating excitability with millimeter-scale precision, surpassing the centimeter-scale focality of TMS and tDCS ([90, 91]; Figure 2). Stimulation is most often applied contralateral to the painful side, enabling access to deep pain-relevant structures and producing significant online/offline analgesic effects with only mild, transient adverse events, underpinned by multiscale mechanisms ranging from ion-channel and synaptic changes to oscillatory and network-level modulation [90, 92–95]. To date, human pain studies typically used focused carriers in the 0.5–0.65 MHz range, with duty cycles spanning ~5%–50% (see Table 1 for full parameter summary) [94, 96].

A 2025 systematic review identified 13 preclinical and human studies using LITUS to target pain-relevant regions, including

the ACC, thalamus, insula, S1/M1, and PAG [94]. Out of those 13, 12 studies demonstrated statistically significant online and/or short-term offline analgesic or antinociceptive effects, including reductions in pain ratings, evoked potentials, and hyperalgesia. For instance, targeting descending pathway structures such as the PAG has demonstrated enhanced neuronal activity with analgesic effects in mouse models [97]. Additionally, Kim et al. [98] showed in mice that LITUS to the S1 and insula reduced heat pain sensitivity, modulated heat/mechanical hyperalgesia and altered behavior and EEG activity. Among human data, a randomized, sham-controlled crossover trial in 20 chronic pain patients found that two sessions of inhibitory LITUS targeting the ACC produced clinically meaningful pain relief in 60% of participants versus 15%–20% with sham, with mean pain reductions of 60%, 43% and 33% immediately, at day 1 and day 7 after stimulation, compared with 14.4%, 12.3% and 6.6% under sham [99].

Current evidence suggests that LITUS can effectively modulate network nodes through inhibition and excitation in both ascending and descending pain pathways, making LITUS an attractive neuromodulation tool for chronic pain with encouraging preliminary evidence and the potential to engage a broader range of (subcortical) targets non-invasively [100]. According to a recent meta-analysis, invasive deep brain stimulation (DBS) for chronic pain achieves significant effects (SMD 1.65; 95% CI 1.31; 2.00), with the VPL, ACC, PVG and PAG emerging as the most effective targets, though with substantial variability across studies [14]. Since DBS is often reserved for highly refractory cases due to procedural complexity, it remains to be seen whether LITUS can potentially mirror such effects.

Key translational barriers still limit clinical scaling of LITUS: skull/hair attenuation and phase aberrations can distort dosing unless measured and compensated [101, 102]; target engagement is often assumed rather than verified, motivating fMRI validation and MR acoustic radiation force imaging (MR-ARFI) to confirm focus and estimate in situ exposure [99, 103]; and heterogeneous parameters/outcomes impede dose–response inference, underscoring the need for standardized reporting and exposure metrics [94]. Accordingly, larger sham-controlled trials with target verification and harmonized protocols are required before firm recommendations can be made.

3.4 | Summary and Next Steps

The three-pathway, network-level framework reviewed in Section 2 provides a useful scaffold for understanding pain pathophysiology, but current NIBS trials still target a relatively small set of population-derived sites within lateral, medial or descending pathways and, on average, yield small-to-moderate, often short-lived analgesia with substantial interindividual variability. Although rTMS has guideline-level support, particularly for neuropathic pain, tES is rarely recommended in practice, and LITUS remains an emerging modality with promising but preliminary evidence. Collectively, these observations suggest that whereas neuromodulation can engage pain-relevant circuits, its clinical impact is still constrained. Next to optimizing trial designs, this arguably needs to be addressed by focusing on "how" and "where" we stimulate. Consequently, precision neuroscience work has increasingly focused on modeling individual brain networks to refine target selection and on personalizing stimulation parameters to reduce variability and enhance effect sizes. These complementary routes to personalization are summarized in Figure 3.

4 | Paths to Personalization

4.1 | Target Personalization and Graph-Theoretical Modeling

Targeting strategies have evolved considerably over recent years. Yet, in most chronic pain NIBS studies and clinical protocols, stimulation sites are still chosen using hypothesis-driven anatomy-based rules, group-average coordinates, or normative seed-based connectivity, implicitly assuming that "consensus" regions (e.g., the sgACC in depression or PAG/M1 in pain) generalize across individuals [11, 104, 105]. Importantly, however, research shows that large-scale network organization is highly idiosyncratic and not always generalizable [106]. Moreover, network dynamics can vary across chronic pain phenotypes [107]. TMS studies suggest that using individual resting-state functional connectivity (rsFC) may improve behavioral and clinical effects relative to purely anatomical or scalp-landmark targets, although most evidence so far is protocol-specific and arises from psychiatric cohorts [10, 108, 110]. A prominent example is Stanford Neuromodulation Therapy for depression, which uses each patient's resting-state fMRI to identify a dlPFC site most functionally anticorrelated with sgACC and combines this with high-dose, accelerated intermittent theta burst stimulation, yielding high acute efficacy in open-label work and superior to sham in a double-blind RCT [10, 108]. However, the relative contribution of dose, spacing and targeting remains unresolved, and the approach is constrained by an a priori sgACC-dlPFC circuit that does not directly translate to pain [11]. In chronic pain, prospective evidence that individual rsFC to consensus regions robustly predicts response to stimulation is still lacking and clinical M1 rTMS studies continue to report limited analgesia despite partial individualization via motor hotspot mapping [26, 62, 111, 112].

More recently, largely at a conceptual and methodological level, several groups have proposed graph-theoretical frameworks, to better capture individual network organization beyond a priori regions of interest, modeling brain regions as *nodes* and functional connections as *edges* using resting-state fMRI to construct an individual functional connectome summarized by whole-system metrics [11, 113–115]. Importantly, these measures do not simply quantify "stronger" or "weaker" connectivity, but the role a region plays within global network topology. For example, they capture how brain regions cluster into communities that are more connected within than between groups (i.e., modularity), typically identified in thresholded rsFC graphs; these communities align with canonical resting-state networks and can be estimated at the individual level with prognostic value for treatment outcomes [11]. They also index local and global communication efficiency and cross-network bridging, including high participation-coefficient "diverse club" hubs with connections

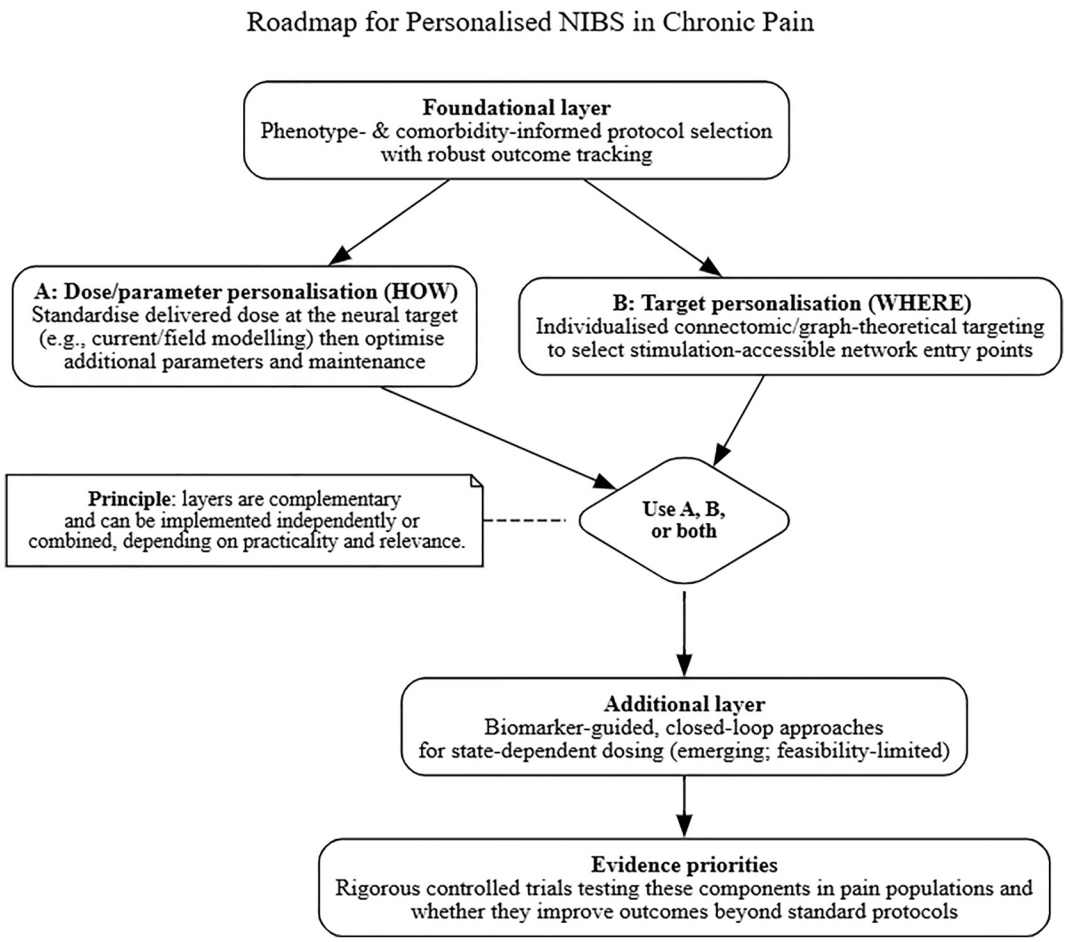

FIGURE 3 | Conceptual roadmap for personalized non-invasive brain stimulation (NIBS) in chronic pain. The figure summarizes a pragmatic, modular framework for translating "personalization" into NIBS practice and trials. Note that this is a summary of the personalization components emphasized in this review and is not intended as an exhaustive list of personalization strategies. A foundational layer establishes phenotype- and comorbidity-informed protocol selection with robust outcome tracking. From this baseline, two complementary personalization components can be implemented independently or combined: (A) dose/parameter personalization ("how"), which aims to standardize delivered stimulation dose at the neural target (e.g., via current-flow or electric-field modeling) and then selectively incorporate additional variability domains to optimize response, including protocol features (e.g., frequency/burst pattern, montage/coil orientation, session spacing and maintenance) and state/susceptibility factors (e.g., baseline neurophysiology and mental state at stimulation); and (B) target personalization ("where"), which uses individualized connectomic or graph-theoretical approaches to construct a person-specific network, quantify node roles (e.g., hubs/bridges), and select anatomically accessible entry points predicted to exert maximal leverage over pain-relevant (sub)networks. An additional, emerging layer involves biomarker-guided closed-loop approaches for state-dependent dosing, which are currently technically and feasibility-limited. Across all components, priority is given to rigorous controlled trials that test these strategies in pain populations and determine whether they improve outcomes beyond standard, protocol-based stimulation.

distributed across modules (for detailed explanation see [11, 114]). Damage to high participation-coefficient nodes disrupts modular architecture [116], and hubs are disproportionately implicated across many brain disorders, including chronic pain [117]. Graph-based studies report alterations in whole-brain topology of pain patients, with evidence for changes in local efficiency and a shifted integration–segregation balance [28]. Moreover, personalized fMRI-guided TMS shows that hub disruption can impair cognition/integration [118], and precision-modeling combining individual rsFC with electric-field simulations suggests the network impact of TMS can be predicted and optimized on a single-subject basis, at least in silico [119]. Together, these findings provide support for the key role of specific hubs in large-scale integration and motivate topology-informed biomarkers and stimulation targets.

For NIBS, the practical appeal of graph-derived features is that they could, in principle, prioritize targets by network leverage. Graph theory can be applied to normative/group connectomes to nominate candidate targets, but also to individual connectomes for true personalization. Rather than stimulating a population-derived coordinate, one could select a stimulation-feasible node that, given the individual's community structure, is positioned to shift communication within and between pain-relevant subnetworks. A plausible, prospective scenario in chronic pain is when a putative pain-maintaining region is subcortical or otherwise poorly reached by conventional NIBS (a constraint that may lessen as depth-capable approaches mature). In such cases, graph-informed targeting could identify an accessible "entry point" whose topology suggests high influence (e.g., bridge/hub properties). For example, in

neuropathic pain associated with aberrant coupling within a sensorimotor–thalamo-cortical circuit, one could (i) derive the individual's sensorimotor community from the resting-state fMRI functional connectome, (ii) restrict candidates to stimulation-feasible nodes within the same broad target territory (e.g., peri-Rolandic cortex) and rank them by cross-network bridging/hub metrics (e.g., participation coefficient) with respect to the pain-relevant subnetwork, and (iii) stimulate the highest-ranking anatomically accessible node within that territory rather than defaulting to a standard M1 hotspot. In this way, targeting is anchored to the individual's network topology and potential downstream reach.

In summary, graph theory provides an interpretable language for describing network dysfunction in chronic pain and translating it into testable targeting rules for personalized stimulation. It can be applied to derive candidate targets and biomarkers from individual neuroimaging, with performance benchmarked against normative/group-derived hubs. However, prospective chronic pain trials that operationalize graph-derived rules for target selection are largely missing, and will likely require multimodal pre/post imaging to quantify network change and verify engagement [11], although practical constraints (imaging burden and pipeline standardization) will likely necessitate staged implementation in specialized settings. Nonetheless, this framework offers a pragmatic path to mechanism- and network-informed candidate targets that can be evaluated in future studies.

4.2 | Parameter Personalization and Closed-Loop Neuromodulation

Beyond “where” to stimulate, “how” stimulation is delivered is itself a major source of variability. For transcranial electrical stimulation (tES) in particular, the parameter space is high-dimensional and nonlinear: intensity, duration, waveform, montage, timing, and session structure interact in ways that challenge simple dose–response assumptions [68, 120]. Non-monotonic effects illustrate this clearly. For example, in motor-cortical tDCS, excitability increases have been reported around 2 mA/20 min, but can be absent at shorter (e.g., 10 min) or longer (e.g., 30 min) durations, and may not scale with higher intensities [121, 122]. Moreover, inter-individual anatomical differences (e.g., CSF thickness) can de-standardize delivered dose, such that the same applied current produces meaningfully different intracranial electric fields across individuals [123, 124].

First personalization efforts in both tES and rTMS often start by accounting for individual differences in anatomy/neurobiology that materially affect the delivered electric field at the cortical target [68, 125]. For tES, structural MRI–based current-flow modeling can be used to scale intensity or optimize montages so that targets such as M1 or dlPFC receive more comparable E-fields across individuals [126]. Direct chronic pain–specific evidence that such modeling improves clinical outcomes, particularly systematic comparisons of model-informed versus non-individualized or sham tES, remains limited. Evidence from other domains includes a multicentre ADHD RCT that delivered multichannel tDCS using a current-flow/E-field–optimized montage and reported significant cognitive effects, but lacked a conventional-tDCS comparator [127]. Separately, a recent depression RCT used structural MRI–guided neuronavigation to individualize HD-tDCS placement over dlPFC, showing greater mood improvement versus sham and suggesting superiority over conventional tDCS [128].

For rTMS, stimulation intensity is typically set as a fixed %RMT, despite RMT's anatomical dependence (e.g., scalp-to-cortex distance), so intracranial exposure can vary markedly across patients, particularly between males and females (and especially at non-motor targets) [129, 130]. Personalized E-field modeling can support target-level dose definition, coil-orientation optimization, and post hoc delivered-dose quantification for dose-response analyses, and can mitigate motion-related variability via online E-field–guided adjustment of stimulator output [131–133]. To date, neuronavigation incorporating E-field estimation has more often supported coil placement and exposure characterization than true E-field normalization [134, 135], and improved spatial targeting/physical-dose precision alone has not ensured efficacy (e.g., navigation-guided M1 rTMS for upper-limb neuropathic pain; connectivity-guided accelerated iTBS to DLPFC for knee osteoarthritis) [110, 136, 137]. Lefaucheur [110] suggests the null findings in Hodkinson et al. may reflect targeting a suboptimal circuit (LDLPFC-rAI) despite connectivity guidance. Overall, pain RCTs that personalize beyond standard motor hotspot mapping or normalize target E-field (vs. %RMT) remain scarce.

For LITUS, individual MRI/CT-based acoustic simulations are a practical route to personalization, allowing focal depth and in situ intensity to be tailored to each person's skull/head geometry [138, 139]. But simulation-based planning benefits from in vivo verification: optimized MR-ARFI can non-invasively confirm focal targeting and estimate exposure at low pressures with motion-robust, short acquisitions, supporting an iterative “plan → measure → adjust” dosing workflow [103]. Consistent with this, pseudo-CT derived from structural MRI has enabled depth-specific theta-burst TUS of human M1 (~5 mm vs. ~16 mm), with continuous theta-burst producing LTD-like reductions in corticospinal excitability, showing the value of matching dose/depth to the individual [140]. In principle, this personalized dose–target planning approach could be extended to pain-relevant (sub)cortical sites, as long as target engagement/exposure is verified (e.g., with MR-ARFI).

Notably, anatomy and neurobiology are only one piece of the personalization puzzle. In personalized modeled electric fields, inter-individual variation accounts for only a limited proportion of observed response variability [122]. More broadly, sources of variability include anatomy, neurophysiology, conductivity, temporal and neurochemical factors, mental state/traits, and genetics [68, 120, 141–143]. For example, psychiatric comorbidities are not merely consequences of chronic pain but can shift the network phenotype that NIBS is attempting to modulate, particularly within salience–DMN–control circuitry. In chronic back pain, comorbid depressive symptoms have been linked to altered network topology (including reduced local efficiency) and connectivity patterns that relate to disability and catastrophising, reflecting a distinct comorbidity-associated network state [144]. Moreover, in fibromyalgia patients with comorbid depression, baseline depression severity moderated the analgesic response to left prefrontal rTMS [145].

Moving forward, a useful organizing distinction is between (i) standardizing physical exposure at the neural target (*what is delivered*) and (ii) personalizing for state, circuit engagement, and susceptibility (*what the brain does with what is delivered*). Recently, van Hoornweder et al. [68] proposed a pragmatic, hierarchical framework for personalization—developed for tES but arguably generalizable to other NIBS modalities, provided modality-specific modeling tools and dosing metrics are used. Applied to chronic pain, this approach may involve to first control major, relatively stable sources of variance, primarily anatomy and baseline neurobiology (e.g., quantified with structural MRI, EEG), and basic clinical profiling, including comorbidities (e.g., depression/anxiety) that can alter pain-related network engagement and treatment response, then layer in more dynamic or costly domains (e.g., circadian/hormonal factors, genotyping, mental state control) only when they add predictive value, as excessive personalization can yield diminishing returns and increase susceptibility to error and overfitting. Accordingly, and given the substantial cost and complexity involved, practitioners may need to prioritize the variability domains most relevant to their specific clinical application [68]. In parallel, streamlining imaging and field-modeling pipelines is essential to make personalization practically scalable.

Finally, within this largely open-loop framework, closed-loop systems represent an additional layer that updates stimulation online to accommodate state-dependent variability, using physiological markers of target engagement from EEG and, in emerging tES–fMRI work, BOLD-derived network biomarkers [146]. In depression, for instance, EEG alpha power has been used to gate tACS trains, yielding reductions in depressive symptoms, whereas closed-loop amplitude-modulated tACS over parieto-occipital cortex enhances working memory by locking stimulation to alpha oscillations [147, 148]. Given well-documented alpha/theta abnormalities in chronic pain, similar EEG-driven tES designs appear transferrable as candidate closed-loop dosing schemes [149]. In invasive chronic pain neuromodulation, patient-specific intracranial mapping and biomarker identification have been used to implement closed-loop DBS driven by activity in cortico-striatal–thalamocortical circuits; a small-cohort study reported ~50% pain reductions versus sham with effects maintained for up to 3.5 years ([15], *preprint*). Such findings provide a proof-of-concept for biomarker-driven, state-adaptive pain neuromodulation, though the approach remains invasive and translation to NIBS faces substantial hurdles. Overall, closed-loop personalization remains technically demanding and largely experimental, limited by biomarker validity, stimulation artifacts that hinder real-time EEG, fMRI latency, and the challenge of robust online optimization, but continued advances make clinically viable implementations increasingly plausible.

5 | Conclusion

Chronic pain can be viewed as a network-level neuroplasticity disorder driven by imbalance among sensory, affective–salience, and descending modulatory systems. In this systems framework, NIBS is best conceptualized as perturbing maladaptive network dynamics rather than targeting a single "pain center." High-frequency M1 rTMS has the most consistent, guideline-supported analgesic effects, especially in neuropathic pain, though these are typically modest and short-lived. By contrast, tES yields small, heterogeneous benefits with low certainty, whereas tACS and tRNS remain largely experimental. LITUS is promising for focal, depth-capable modulation but needs more trials, improved control of skull-related variability, target verification, and dosing standardization before firm recommendations.

Across modalities, high interindividual variability potentially reflects reliance on population-derived targets and protocol-based dosing that ignore individual network organization, delivered dose at the neural target, state dependence, and frequent comorbidities that may alter treatment response. Translating "personalization" into practice therefore requires a pragmatic framework (Figure 3): a foundational layer of phenotype- and comorbidity-informed, controlled protocol selection with robust outcome tracking; and, as complementary components that can be implemented independently or combined, parameter personalization that standardizes delivered dose (e.g., via current/field modeling) and selectively incorporates additional variability domains to constrain the parameter space, alongside emerging connectomic/graph-theoretical targeting to select stimulation-feasible nodes that best regulate the individual's (sub)networks; and, where feasible as technologies mature, biomarker-guided closed-loop approaches for state-adaptive dosing. Although personalization offers no guarantee of success and will require substantial further research, NIBS is unlikely to realize its full potential for chronic pain without at least some move toward personalized approaches.

Author Contributions

Fabian Broecker: conceptualization, literature review and curation, writing – original draft, writing – review and editing, and figure/table preparation. **Sven Vanneste:** conceptualization, literature review, writing – original draft, writing – review and editing, and supervision. Both authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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