

Electroencephalography research in neuropathic pain (Review)

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Abstract. Neuropathic pain (NP), arising from lesions or dysfunction of the somatosensory system, remains a major clinical challenge due to its subjective and multi-dimensional nature. Traditional pain assessments rely on self-report scales, which lack objectivity and reproducibility. Electroencephalography (EEG), with its high temporal resolution and accessibility, provides a promising avenue for identifying candidate neurophysiological biomarkers of pain. The current narrative review integrates mechanistic insights and electrophysiological evidence to delineate EEG alterations in NP. Resting-state θ increases and dominant-frequency slowing are relatively recurrent in chronic NP, whereas α -, β - and γ -band findings remain heterogeneous. Network analyses further reveal aberrant prefrontal-limbic and sensorimotor connectivity, as well as altered cross-frequency coupling, but the direction and topology of these findings remain dependent on the patient population, recording configuration and analytical metric. Advances in computational EEG analysis, graph theory and machine learning are facilitating exploration of objective, individualized pain assessment frameworks. Emerging portable EEG and multimodal approaches may provide opportunities for future clinical translation. Overall, EEG offers a feasible and dynamic method to bridge subjective pain perception with measurable neurophysiological signatures, paving the way toward precision diagnostics and neuromodulation in NP.

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1. Introduction

Neuropathic pain (NP) is a chronic pain syndrome caused by damage to the peripheral or central somatosensory nervous system, often manifesting as symptoms such as burning, stabbing and hyperalgesia (1-4). Subjective scales such as the visual analogue and numerical rating scales (5) are affected by emotional, cultural and communication factors, limiting consistency and applicability to infants, young children and patients with cognitive or consciousness impairments (6-9). This limitation has prompted the search for more objective, real-time and widely applicable pain assessment methods.

Electroencephalography (EEG) is currently considered the most promising objective pain biomarker technology due to its millisecond temporal resolution, ability to capture simultaneous data across brain regions, portability and low cost (10,11). Several studies have reported partially reproducible EEG patterns in acute and patients with chronic NP; however, the strength of evidence differs markedly across findings and numerous findings rest on small, heterogeneous cohorts: These findings include increased prefrontal cortex (PFC) θ power (12), a downward shift of the peak α frequency (PAF) toward lower frequencies (13-15) and a negative correlation between low-frequency β power and pain scores (16). Following this, machine-learning approaches integrating

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multi-frequency EEG features have demonstrated promising performance in pain-related classification and prediction tasks; however, these findings are primarily derived from exploratory studies and require independent validation (17,18). Given the inherent limitations of subjective rating scales and the rapid development of EEG technology, the present article aims to critically synthesize the progress of EEG research related to NP, focusing on: i) Integrating different frequency band features with pain mechanisms and proposing a unified neural regulation model; ii) exploring the clinical translation path of complementing subjective pain assessment with objective EEG-derived measures; and iii) emphasizing the potential application and current limitations of multimodal integration and machine learning in pain assessment (12,19,20). The present review aims to provide a neurophysiological basis for accurate diagnosis and personalized analgesia, and to suggest the direction for future research.

2. Mechanisms of NP

Research on NP originated from the gate control theory, which posits that a 'gate' system composed of substantia gelatinosa (SG) and transmission cells in the dorsal horn of the spinal cord regulates pain transmission: A β fibers activate SG cells, closing the gate and blocking the ascending pain sensation; whereas C and A δ fibers inhibit SG cells, opening the gate and facilitating pain transmission (21). Transcutaneous electrical stimulation activates A β fibers, closing the spinal gate and enhancing cortical control by descending pathways such as the periaqueductal gray (PAG) matter, with EEG showing increased α power in the prefrontal and parietal lobes, indicating pain relief by descending inhibition (22). Decreased β wave power and weakened θ - γ cross-frequency coupling after spinal cord stimulation (SCS) treatment reflect the inhibitory effect of cortical hyperexcitability after gate closure (23). However, this theory primarily focuses on the spinal cord level and fails to explain the multidimensional mechanisms of complex conditions such as chronic pain and phantom limb pain.

Beyond spinal gating, current understanding of NP emphasizes peripheral and central sensitization as core pathophysiological mechanisms. Peripheral sensitization involves lowered nociceptor thresholds, ectopic discharges and altered ion channel expression following nerve injury (24). Central sensitization is characterized by increased excitability and the synaptic efficacy of neurons in central nociceptive pathways, mediated in part by N-methyl-D-aspartate receptor activation, loss of γ -aminobutyric acid (GABA)-mediated inhibitory interneuron function and glial cell-driven neuroinflammation (25,26). Notably, neuroinflammatory processes, including microglial and astrocytic activation and the release of pro-inflammatory cytokines (for example TNF- α and IL-1 β), not only maintain but also amplify central sensitization, thereby contributing to the chronification of NP (26,27).

At the supraspinal level, the thalamocortical dysrhythmia (TCD) model provides a direct mechanistic link between NP pathophysiology and EEG signatures. Llinás *et al* (28) proposed that deafferentation or excessive inhibition of thalamic relay neurons shifts their firing mode from tonic to low-threshold calcium spike bursting, generating persistent θ -range (4-8 Hz)

oscillations that propagate to cortical areas through thalamo-cortical resonance. This model is supported by EEG studies demonstrating that patients with NP exhibit increased cortical θ power and enhanced θ - γ coherence compared with healthy controls (28,29). Thus, TCD offers a neurophysiological framework that directly accounts for the elevated θ activity and altered cross-frequency coupling reported in selected NP cohorts.

Furthermore, dysfunction of the descending pain modulatory system, particularly the PAG-rostral ventromedial medulla pathway, contributes to the maintenance of chronic NP by shifting the balance from descending inhibition toward facilitation (30). These peripheral, spinal and supraspinal mechanisms are not mutually exclusive; rather, they interact in a multi-level cascade that ultimately shapes the cortical oscillatory patterns detectable by EEG. The relationship between these mechanisms and EEG signatures may differ depending on whether the NP originates from peripheral (for example diabetic neuropathy and postherpetic neuralgia) or central (for example spinal cord injury and multiple sclerosis) etiologies, as peripheral NP is primarily driven by ectopic peripheral input and peripheral-central sensitization, while central NP more directly reflects intrinsic thalamocortical network disruption (29,31).

To overcome the limitation of these mechanisms in fully explaining the multidimensional nature of pain, the neuromatrix theory was proposed, emphasizing that pain is the result of dynamic integration of a distributed thalamic-limbic-cortical network (32-34). It posits that excessive θ synchronization between the ventroposterior thalamic nucleus (VPN) and primary somatosensory (S1) cortex amplifies spinal input while weakening prefrontal thalamic inhibition, leading to hypersensitivity; an EEG study reported that increased VPN-S1 θ - γ coupling and altered PFC-anterior cingulate gyrus (ACC) connectivity may reflect pain amplification and network imbalance (23). Thus, the neuromatrix theory offers a more systematic neural network perspective than gate control, providing a new explanatory framework for complex pain conditions, such as chronic pain and phantom limb pain (Fig. 1).

Building on this, the biopsychosocial model further expands the scope of pain mechanisms, incorporating psychological states and social environments into the regulatory system (35-37). Physiologically, acute pain is primarily driven by spinal gate mechanisms, while chronic pain stems from dysregulation of the cortical-thalamic circuitry (31,38). Psychological factors such as anxiety and depression weaken descending inhibition from the PFC to the thalamus (39), leading to increased θ wave power and concomitant weakened ACC-insula functional connectivity. Conversely, social support or positive interventions (such as exercise and mindfulness meditation) can activate the ventral striatum-PFC reward circuitry, enhancing descending inhibition. EEG results show increased occipital and parietal α wave power, which correlates with decreased pain scores (35,37). This model combines physiological, psychological and social three-dimensional mechanisms with electrophysiological indicators, which not only deepens the understanding of the multi-source control of pain experience, but also provides a theoretical basis for multimodal EEG biomarkers and personalized monitoring.

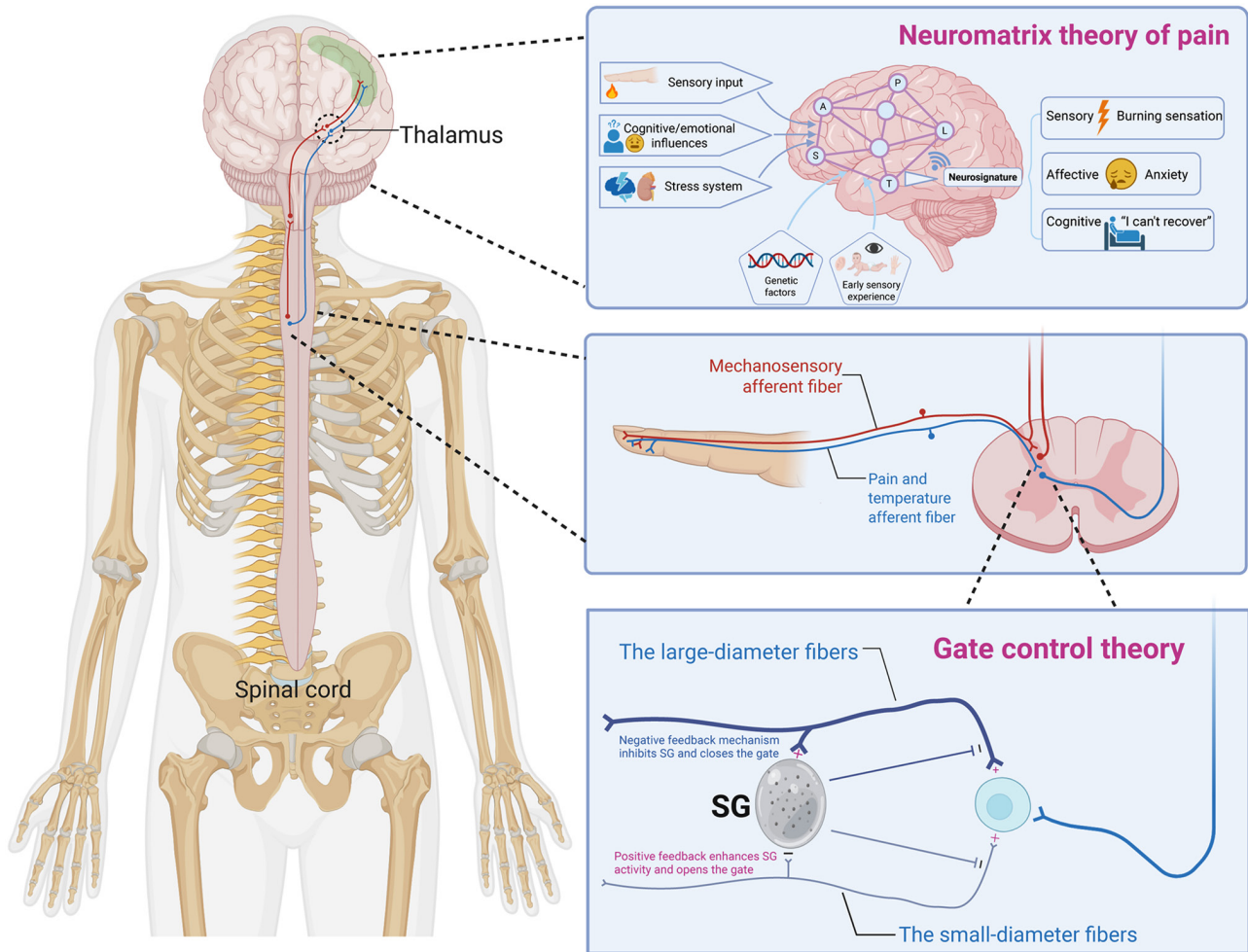


Figure 1. Multidimensional mechanisms of pain, encompassing sensory-discriminative, affective-emotional and cognitive-evaluative components. These dimensions interact by ascending and descending pathways linking peripheral nociceptors, the thalamus, somatosensory cortex and limbic structures, jointly shaping the subjective experience of pain. Brain regions are labeled as follows: A=anterior cingulate cortex, P=posterior parietal cortex, L=limbic system, S=primary/secondary somatosensory cortex and T=thalamus. Created in BioRender. serein, L. (2026) <https://BioRender.com/v0u86zc>. SG, substantia gelatinosa.

3. Overall status of EEG in pain research

Pain types and study designs. EEG research relevant to NP primarily includes studies of clinically defined chronic NP, together with complementary evidence from broader chronic-pain cohorts and experimental, acute or postoperative pain paradigms. The latter provide mechanistic context but should not be considered direct evidence of chronic NP biomarkers (1-4). In chronic pain cohorts resting-state EEG is often utilized to capture long-term plasticity (40-42). By contrast, studies of acute/postoperative pain are often based on task paradigms or noxious stimulation, often observing α/β desynchronization and increased θ - γ coupling induced by painful events (43-46). A Cleveland Clinic team further utilized sub-second features to achieve classification and identification of healthy controls, chronic pain and postoperative pain, achieving markedly improved accuracy than traditional metrics (18). However, current studies are generally limited by small sample sizes and design heterogeneity: >60% of resting-state EEG studies have <30 subjects and experimental protocols vary markedly in terms of electrode placement and stimulation conditions, limiting the comparability of results (47-49).

Methodological key points. Methodologically, pain-related EEG research still lacks unified standards. Electrode configurations range from traditional 19-channel 10-20 systems to high-density 64-channel solutions; sampling rates vary from 256 Hz to 1 kHz, directly impacting the comparability of frequency band partitioning and connectivity analysis (48). Artifact control remains crucial for reliable analysis. Common interferences include myoelectricity, eye movements and power-frequency noise. A previous study proposed combining an algorithm based on the analytic signal envelope with non-linear measures for artifact removal and utilizing instantaneous entropy and spectral information entropy to improve real-time monitoring stability (50). In terms of feature extraction, power spectral density (PSD) and α/θ and β/δ ratios remain commonly used indicators (51). However, features such as cross-frequency coupling, network topology and non-linear entropy are being increasingly introduced to enhance discriminative power (52,53). Numerous studies have called for the development of unified acquisition and analysis protocols, the construction of a Brain Imaging Data Structure-compatible database and the validation of the universality and clinical efficacy of EEG biomarkers using large multicenter sample sizes (54-56). Furthermore, systematic evaluation of electrode

placement and calibration strategies for children and the elderly is lacking, and further research is urgently needed (57,58).

4. Characteristics of pain-related EEG frequency bands

Before considering individual frequency bands, their evidence maturity should be distinguished. Increases in resting θ activity and slowing of dominant θ - α frequency are among the more recurrent observations in chronic NP. By contrast, δ and α power, β -sub-band activity, γ oscillations and connectivity measures show greater dependence on pain phenotype, recording state and analytical approach. Associations should be interpreted based on the strength and consistency of available evidence, as the degree to which these findings have been established varies across EEG measure (59).

δ . To the best of our knowledge, research on the role of δ oscillations in NP is limited. Patients with central NP associated with multiple sclerosis exhibit decreased δ relative power, suggesting that reduced δ activity may be a specific signal of the pain phenotype (40). Further analysis has revealed a negative correlation between δ power in the central region and subjective pain intensity, supporting the ‘ δ reduction leads to pain relief’ hypothesis (60-62). However, a study reported elevated δ and θ , accompanied by α suppression, in the context of chronic pain, which has been interpreted as a compensatory mechanism for maintaining homeostasis in the cortical-thalamic network (51). Overall, δ activity may indicate hypothalamic-cortical inhibition or adaptive regulation to sustained stimulation, with patterns varying by etiology, population and analytical approach (63-65). Future studies with large, multicenter cohorts are needed to clarify the spatiotemporal characteristics and clinical significance of δ activity.

θ . Increases in resting θ activity are among the more recurrent group-level findings in chronic NP, although their regional distribution and associations with pain intensity vary across studies (40,66). Regional differences are notable, with increased parietal θ linked to lower pain perception, suggesting an ascending inhibitory mechanism (67). In patients with central NP, abnormalities in θ activity within the frontal-thalamic network are closely associated with pain persistence (68). Mechanistically, θ oscillations may have a dual role, with their enhancement interpreted as a compensatory response characterized by elevated δ/θ and concurrent α inhibition (51). Enhanced θ oscillations may represent pathological hypersynchrony resulting from a prefrontal-thalamic imbalance (69). Functionally, the coupling between θ phase and γ amplitude in the thalamic-S1 circuit is enhanced during pain and attenuated following SCS (23). A deep brain stimulation (DBS) study has also demonstrated that reductions in θ activity correlate with the analgesic effect of DBS (70). Furthermore, machine learning models based on prefrontal θ power can differentiate pain severity, providing a methodological basis for clinical EEG quantification (52). In summary, θ oscillations may contribute to pain-related processing yet their dual compensatory-pathological role awaits further clarification through longitudinal studies.

α . Across experimental and chronic-pain studies, α -band findings encompass two distinct spectral measures: Peak α frequency (PAF) and α -band power. Studies have demonstrated that decreased PAF is associated with increased pain sensitivity; whereas, effective SCS responders exhibit increased PAF and a rebound in α power, suggesting that these measures may serve as candidate markers of treatment response (13-15,71). The direction of power varies: Some studies have revealed increased α power in patients with chronic pain (40,72), while another study reported a negative correlation with pain intensity (73). The direction of α power change is notably inconsistent across studies, with both increases and decreases reported in chronic pain. A recent large-scale mega-analysis highlighted the potential contribution of sample characteristics and methodological heterogeneity to limited cross-dataset replicability (59). Several specific factors may contribute to both the inconsistent direction of α -power changes and their limited replicability across studies, including differences in: i) Spectral quantification (absolute vs. relative power); ii) α sub-band definitions (low- vs. high- α); iii) recording state, since α power is strongly modulated by the eyes-closed vs. eyes-open condition (74); iv) pharmacological effects, as analgesic and psychoactive medications directly alter parieto-occipital α oscillations (75); v) reference montage and sensor- vs. source-level analysis; and vi) phenotypic heterogeneity with comorbid anxiety or depression. In addition, fixed-frequency α definitions may not fully capture individual variability in α peak location, potentially contributing to differences among studies using fixed vs. individualized α -band approaches. Furthermore, conventional α -power estimates may combine periodic α oscillations with changes in the aperiodic 1/f background (76). Disentangling these factors will require standardized acquisition protocols and larger, phenotypically homogeneous cohorts (77,78). Regionally, selected multiple sclerosis cohorts with pain symptoms exhibit decreased relative α power (68), whereas patients with postherpetic pain have demonstrated increased α power and prefrontal coherence during neurostimulation (79). A functional connectivity study reported α -band network alterations in selected cohorts; however, these findings do not establish low α power as a key characteristic of NP networks (80). Overall, lower PAF may be relevant to pain sensitivity, whereas α -power alterations appear bidirectional and context dependent. Their utility for monitoring treatment response or supporting etiological classification remains to be established.

β . Patients with chronic pain often exhibit an upward shift in the dominant β peak frequency, accompanied by a decrease in the dominant θ - α frequency, although the consistency and functional significance of this pattern remain uncertain (40). Resting-state EEG reveals that prefrontal β power asymmetry can differentiate pain severity (52). β power and approximate entropy are markedly elevated in patients with severe pain, but their value for severity classification or prediction has not been independently established (67). Low-frequency β abnormalities (13-20 Hz), primarily localized to the frontal and left cortical regions in selected cohorts (81-83), are mechanistically associated with imbalances in the ACC-S1 pathway (69). Low-frequency β power is negatively associated with pain intensity scores and is considered an indicator of impaired

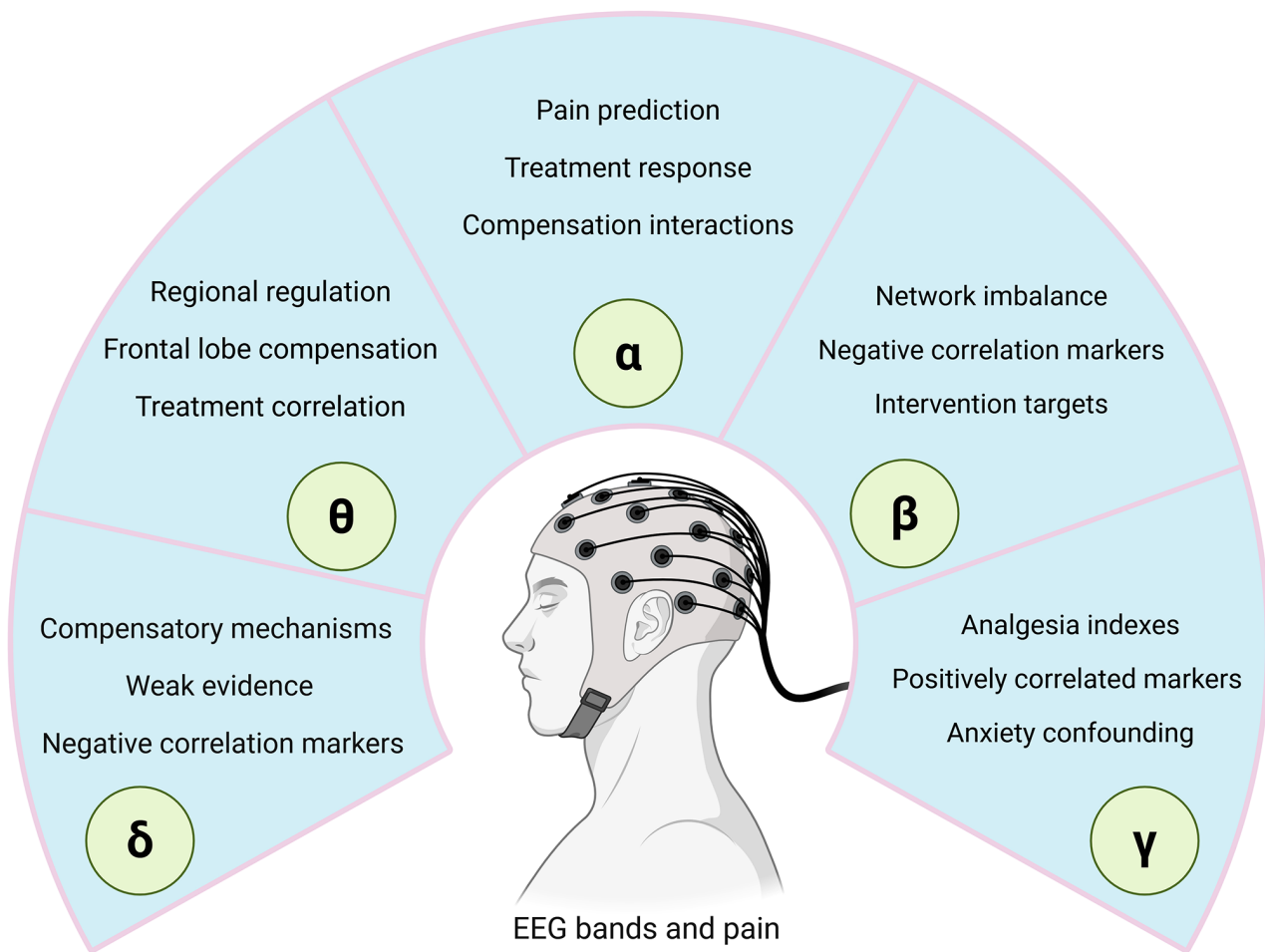


Figure 2. Schematic representation of major EEG frequency bands (δ , θ , α , β and γ) and their functional significance in pain processing. Alterations in these oscillations, such as increased θ and decreased α or β power, reflect disrupted sensory and affective integration in chronic pain states. Created in BioRender. serein, L. (2026) <https://BioRender.com/colt5k3>. EEG, electroencephalography.

GABAergic inhibitory function (16). Preclinical and interventional studies provide preliminary evidence that β activity may change during pain modulation. In animal models, Fe^{2+} nanoparticles can modulate β waves and affect pain behavior (84). Clinical DBS studies indicated that thalamic β oscillation dynamics change synchronously with pain relief, suggesting that it may serve as a feedback signal for closed-loop regulation (85). However, β -band findings appear to depend on the analyzed sub-band, brain region and clinical population, and the functional division and longitudinal dynamics of the β sub-bands remain poorly characterized (16,86).

γ . γ oscillations have been implicated in nociceptive processing and attentional modulation, particularly in experimental pain studies (87,88). Elevated resting-state γ activity has also been reported in selected chronic NP cohorts and has been associated with subjective pain ratings (89). Source localization findings have implicated the S1 and insula, potentially reflecting altered nociceptive processing within the S1-insula pathway. Interventional studies have demonstrated that γ activity may be modifiable. Dorsal root ganglion stimulation has been associated with reductions in γ power and the degree of analgesic response (90). Responders to SCS also exhibit γ suppression accompanied by an increase in α power, reflecting a rebalancing

of neural activity (71). Rodent models have further demonstrated that S1 γ phase encoding can directly drive pain avoidance behavior (87). At the network level, γ power asymmetry can differentiate pain levels and serves as an effective feature for classification in support vector machine models in an individual cohort (52). Thalamus-S1 θ - γ coupling is reduced after analgesic intervention, suggesting that γ is also regulated by cross-frequency mechanisms (23). Although γ oscillations are implicated in nociceptive processing in experimental pain studies (87,91), their reproducibility and clinical specificity in chronic NP remain uncertain (89). Notably, γ activity is associated with anxiety and depression in patients with chronic NP (89). Therefore, future studies should strictly control for affective comorbidities and integrate multi-channel source imaging to delineate the cortical-cortical and cortical-thalamic pathways of γ oscillation. Fig. 2 summarizes the major EEG frequency-band alterations and their functional significance in pain processing.

5. Network connectivity and cross-frequency coupling

Functional connectivity. Resting-state EEG studies have reported altered functional connectivity in chronic pain and NP cohorts, including changes involving prefrontal-affective,

sensorimotor and thalamocortical networks (40,41,47,92). Systematic reviews have summarized heterogeneous findings across frequency bands and connectivity metrics, without identifying a consistently replicated set of altered connections specific to NP (40,41). Decreased α - or β -band coherence and phase-locking value between prefrontal regions and the insula or anterior cingulate cortex have been reported in selected cohorts, with some studies also reporting associations with pain duration or comorbid anxiety (22,88). A high-density EEG- current source density study has further confirmed that patients with chronic low back pain exhibit decreased connectivity between the left middle temporal gyrus and the posterior cingulate gyrus in the β band, which are negatively associated with pain levels (42). Alterations in sensory-affective connectivity have also been reported, although their direction varies across networks and analytical measures (47,93). The thalamus-S1 network exhibits hypersynchrony in the θ band, considered an ‘amplification of nociceptive input’, while notably decreased thalamus-insula θ coherence suggests impaired pain processing (22,92). Patients with multiple sclerosis and migraine also exhibit elevated frontal θ power accompanied by decreased phase-locking value (PLV) between ACC and insula, reflecting a dysregulation of attention-emotion regulatory balance (22). These observations provide complementary evidence regarding pain-related network alterations but should not be interpreted as a NP-specific connectivity signature. Notably, a support vector regression model based on 64-channel EEG data revealed that prefrontal β asymmetry and β - γ phase-amplitude coupling (PAC) explained ~65.5% of the variance in chronic NP severity, highlighting the importance of the prefrontal-affective network in neural encoding of pain (52).

Overall, network imbalances in chronic pain appear to unfold through a cascading sequence of dysfunctions. Altered top-down regulation and disrupted synchronization between sensory and affective circuits may contribute to pain persistence and its association with emotional distress. However, the direction and causal organization of these network alterations remain uncertain. Future studies combining metrics robust to volume conduction (such as debiased weighted phase lag index) with source localization will delineate the effective connectivity between deep structures (such as the PAG) and cortical nodes.

Cross-frequency coupling. PAC reflects the modulation of high-frequency amplitude by the phase of low-frequency oscillations and is considered a mechanism for pain regulation. Thalamus-S1 θ - γ PAC is elevated in chronic pain and normalizes with analgesic treatment, indicating its role in nociceptive amplification and gating (23). In patients with chronic NP during eyes-open resting-state EEG, frontal low- β phase-low- γ amplitude PAC asymmetry is negatively associated with pain severity (52). When SCS induces analgesia, patients demonstrate increased α power and restored α - β synchronization, suggesting that α - β remodeling serves as a marker of network remodeling (71). Thus, alterations in cross-frequency interactions and oscillatory synchronization may reflect pain-related network dysregulation and its modulation by analgesic treatment.

Frequency-network composite biomarker (FNCB): A conceptual framework. Single frequency bands or connectivity metrics are often unstable due to individual heterogeneity, task conditions and emotional comorbidity (86,94-96). Therefore, the FNCB is proposed as a conceptual framework for organizing existing multidimensional EEG evidence. However, the FNCB has not yet been prospectively validated as a single integrated biomarker. FNCB integrates multi-band power, peak frequency and ratios with key connectivity metrics (such as coherence, PLV and PAC) as a conceptual approach to improve the characterization of pain phenotypes and therapeutic responses (18).

Previous studies provide proof-of-concept support for combining multiple EEG features. Ryu *et al* (52) reported that a support vector regression model combining prefrontal β asymmetry, low β -low γ PAC and θ power effectively predicted pain severity. Another study used β power, approximate entropy, α/θ ratio and PLV as input features for a random forest model, achieving 85% classification accuracy (67). In an intervention study, changes in α power and α - β coupling in SCS responders were associated with analgesic efficacy (71). These observations provide preliminary support for longitudinal composite-feature approaches.

Based on the aforementioned reviewed evidence, we propose a three-step framework for implementing FNCB:

Step i): Spectral-connectivity dual-domain feature extraction. Single-domain features, whether spectral power alone or connectivity metrics alone, are vulnerable to individual heterogeneity and emotional comorbidity (86,94-96). However, combining spectral features (for example θ power, PAF and β asymmetry) with connectivity metrics (for example PLV, coherence and PAC) captures complementary information about both local oscillatory dynamics and large-scale network reorganization. This rationale is empirically supported by studies showing that models incorporating both domains outperform single-domain approaches: Ryu *et al* (52) demonstrated that integrating prefrontal β asymmetry with low β -low γ PAC and θ power explained 65.5% of pain severity variance, while Pritchep *et al* (23) demonstrated that combining spectral and source-localized connectivity features improved discrimination of pain states. Therefore, dual-domain extraction is a necessary first step to ensure that FNCB captures the full complexity of pain-related neural alterations.

Step ii): Feature selection and model integration under cross-validation. Given the high dimensionality of dual-domain feature sets, systematic feature selection is key to avoid overfitting and identify the most discriminative biomarker combinations. Cross-validated ensemble strategies, such as stacking random forest with support vector regression, leverage the complementary strengths of different algorithms: Tree-based methods handle non-linear feature interactions and provide feature importance rankings, while regression models optimize continuous pain severity prediction (52,67). This approach has been validated in pain EEG studies, where random forest models using β power, approximate entropy, α/θ ratio and PLV achieved 85% classification accuracy under cross-validation (67), and machine learning pipelines combining multiple classifiers have been demonstrated to improve generalizability in EEG-based pain detection (18).

Step iii): Dynamic monitoring and threshold mapping. To bridge the gap between model outputs and clinical decision-making, raw classifier predictions must be translated into interpretable metrics. Threshold mapping converts continuous model outputs into clinically meaningful pain probability scores or graded categories (for example mild, moderate and severe), analogous to established clinical indices such as the Bispectral Index used for anesthesia depth monitoring (97). This step is critical as clinicians require actionable, interpretable outputs rather than abstract feature weights. Furthermore, dynamic monitoring enables longitudinal tracking of pain trajectories and treatment responses, as demonstrated by a study showing that α power recovery and α - β coupling restoration in SCS responders can serve as real-time efficacy indicators (71). Thus, threshold mapping represents a potential step toward translating computational outputs into clinically interpretable metrics, although clinically validated thresholds have not yet been established.

Future studies should validate the reliability of this framework across devices and disease types in multicenter cohorts and explore its application in real-time feedback for closed-loop neuromodulation.

6. EEG and electrophysiological changes following central neuromodulation for pain

Since the PFC, cingulate cortex and periventricular grey (PVG)/periaqueductal gray (PAG) are the principal targets of central neuromodulation for refractory pain, the electrophysiological changes recorded after implantation are a natural extension of the aforementioned resting-state and evoked EEG abnormalities. The most direct scalp-EEG evidence comes from epidural motor cortex stimulation (MCS): Using 128-channel EEG, patients with NP show a spatially restricted and attenuated post-movement β synchronization over the affected hemisphere, and chronic MCS restores this defective β rebound in parallel with its analgesic effect, suggesting that MCS acts by re-establishing deficient sensorimotor inhibitory control (98). Convergent evidence from non-invasive stimulation shows that high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex, the technique for which the strongest recommendation exists in NP, restores defective intracortical inhibition in the same patient population (99,100). Deep electrodes allow the complementary, subcortical view. Postoperative local field potentials (LFPs) recorded from the sensory thalamus and PVG/PAG in patients implanted for NP show that: i) θ , α and β oscillations covary with the degree of pain relief; ii) thalamic 17-30 Hz and PVG/PAG 8-12 Hz activity track reported pain intensity; and iii) oscillatory states before stimulation predict subsequent DBS outcome (70,101). Stimulation of one node reciprocally modulates the other, with PAG/PVG stimulation suppressing thalamic δ - β power and thalamic stimulation increasing PAG/PVG δ and θ power (102). For the cingulate target, magnetoencephalography (MEG) in a patient treated with ACC-DBS for whole-body pain demonstrated stimulation-related activity changes across pain-related regions and reorganization over one year of stimulation (103), while chronic ambulatory intracranial recordings from the ACC and orbitofrontal cortex have demonstrated that sustained orbitofrontal power

changes predict individual chronic pain severity, dissociating from the more transient anterior cingulate signatures of acute evoked pain (104). Taken together, restoration of physiological sensorimotor β , normalization of thalamic θ - α activity and prefrontal power changes are as candidate objective markers of therapeutic efficacy and as feedback signals for closed-loop neuromodulation. These data should nevertheless be interpreted cautiously: Cohorts are small or single-case, recording modalities are heterogeneous (scalp EEG, MEG, LFP and intracranial EEG), stimulation artefacts complicate analysis and prospective validation of these candidate biomarkers are still lacking.

7. Objective EEG assessment technology route

Building on previous studies, we propose a four-stage hierarchical conceptual framework outlining potential future pathways for EEG-based pain assessment (Fig. 3). It should be noted that EEG is not the only candidate biomarker modality for NP; blood-based biomarkers (for example cytokines and neurofilament light chain), neuroimaging [functional MRI (fMRI) and positron emission tomography] and autonomic measures each offer complementary information (105,106). However, EEG provides unique advantages in this context, namely: i) Millisecond temporal resolution that captures dynamic oscillatory changes; ii) non-invasiveness; iii) portability suitable for bedside and home monitoring; and iv) relatively low cost, making it a promising candidate for future real-time, longitudinal pain monitoring applications across diverse clinical settings (10,11). The proposed framework comprises four progressive stages: i) Candidate feature evaluation and exploratory threshold assessment; ii) machine learning and deep learning classification; iii) multimodal fusion; and iv) future wearable closed-loop platforms. Stages III and IV (multimodal fusion and wearable closed-loop platforms) remain aspirational and are presented as future directions rather than established practice.

Stage i): Candidate feature evaluation and exploratory threshold assessment. Resting-state or task-based EEG spectral and functional-connectivity measures can be evaluated as candidate screening-oriented features. In patients with chronic NP, frontal lobe θ power has been reported, although the regional distribution and associations with pain intensity vary across studies (16,40). Abnormal α -band dynamics, such as reduced peak α frequency or a low α / θ ratio, may serve as indicators of heightened pain sensitivity, while disrupted coherence across cortical and subcortical circuits networks reflects imbalance in pain-related processing (22,107-109). Weighted integration of these candidate indicators may improve discrimination in exploratory studies, although its reproducibility across populations remains unclear (42,52). Future threshold development will require prespecified training and validation procedures, calibration across NP etiologies and populations, and prospective evaluation of clinical utility (41,88).

Stage ii): Machine learning/deep learning. With the accumulation of large samples and increased computing power, feature engineering extracts information from multiple dimensions, including the time domain (amplitude and Hurst exponent), the frequency domain (PSD and frequency band ratio), non-linearity (sample entropy and approximate entropy)

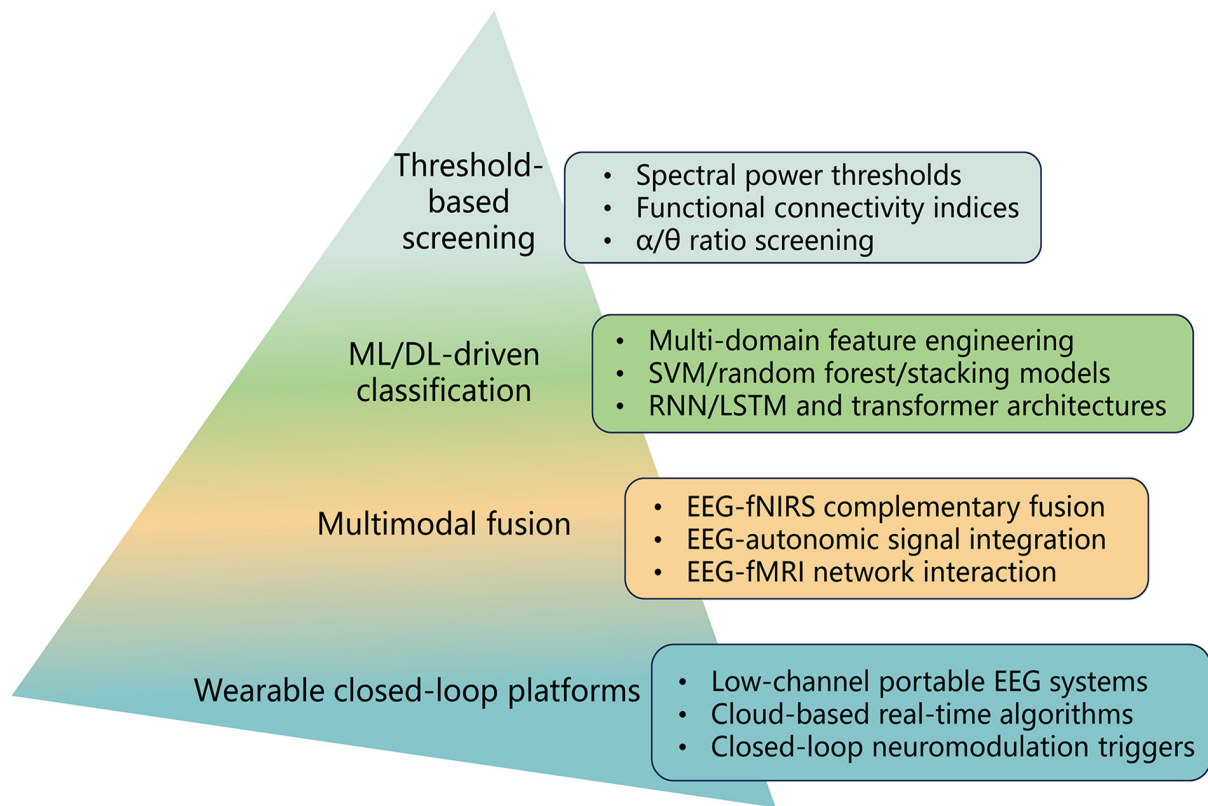


Figure 3. Proposed four-stage hierarchical framework for translating EEG-based pain biomarkers into clinical practice. Stage 1 employs spectral power and connectivity thresholds for rapid screening. Stage 2 leverages ML and DL algorithms for multi-dimensional feature classification. Stage 3 integrates EEG with complementary modalities (fNIRS, fMRI and autonomic signals) to enhance diagnostic robustness. Stage 4 envisions portable, low-channel EEG systems coupled with cloud computing and closed-loop neuromodulation for real-time, personalized pain management. EEG-based approaches are intended to complement, rather than replace, other biomarker modalities such as blood-based and neuroimaging markers. The figure was created using Microsoft PowerPoint. EEG, electroencephalography; fMRI, functional MRI; fNIRS, functional near-infrared spectroscopy; LSTM, long short-term memory; ML, machine learning; DL, deep learning; SVM, support vector machine; RNN, recurrent neural network.

and graph topology (node strength, clustering coefficient and global efficiency) (51,52). Based on this, support vector machines, combining prefrontal β asymmetry, low β -low γ PAC and θ power, have been reported to explain 65.5% of the variance in pain severity within individual cohorts (52). Random forests, integrating β power, approximate entropy, the α/θ ratio and PLV, have achieved classification accuracies of 85% under cross-validation settings in specific datasets (67). Furthermore, recurrent neural network/long short-term memory architectures, together with transformer models may improve predictive performance in larger datasets through approaches such as data augmentation and transfer learning, although their clinical generalizability remains to be established (53). However, these encouraging findings should be interpreted in light of the methodological constraints that currently limit their clinical translation. Despite promising accuracies, current machine learning studies in pain EEG share methodological limitations. Sample sizes are typically small, which inflates apparent performance. Reviews of neuroimaging classification show that small samples systematically bias cross-validated accuracy estimates and produce large error bars (110,111). In high-dimensional EEG analyses, limited sample sizes also increase susceptibility to model overfitting, potentially reducing performance when models are applied to previously unseen data. Reported metrics such as 65.5% variance explained or 85% classification accuracy are derived

almost exclusively from internal cross-validation, whereas rigorous validation requires independent external cohorts and limited sample sizes are known to compromise the reliability of such validation (112). Additional risks include information leakage during feature selection, which further inflates connectome- and EEG-based prediction performance (113), class imbalance and limited model interpretability. Accordingly, current results should be regarded as preliminary and future work must prioritize large multicenter datasets, pre-registered pipelines, independent external validation and evaluation of model calibration and incremental clinical utility.

Stage iii): Multimodal fusion. Combining EEG with autonomic neural signals such as skin conductance can enhance classification robustness (114). EEG-functional near-infrared spectroscopy fusion leverages the complementary temporal and spatial resolutions to improve classification performance by 10-15% (115,116). EEG-fMRI reveals dynamic network interactions among pain-associated brain regions (117). Multimodal strategies may not only improve classification performance but also provide new insights into integrating EEG with other physiological signals.

Stage iv): Future wearable and closed-loop platforms. Low-channel-count (<8 channels) portable EEG systems combined with cloud-based algorithms have been deployed in both intensive care unit (ICU) and home settings (118). Wireless devices based on the ADS1299 chip can achieve

near-laboratory signal-to-noise ratios and reduce the detection latency using early warning algorithms (119,120). Closed-loop neurophysiological systems have been explored in several neurological and physiological applications, demonstrating the feasibility of integrating signal acquisition with adaptive intervention strategies (121-124). In NP, future studies may investigate whether validated EEG-based features could contribute to adaptive neuromodulation approaches; however, such systems remain hypothetical and require notable prospective validation before clinical application.

8. EEG-based assessment of nociception in comatose and non-communicative patients

Self-report, the reference standard for pain assessment, is unavailable for patients who are comatose, sedated or in prolonged disorders of consciousness (DoC), yet the absence of an overt behavioral response does not exclude cortical nociceptive processing. Behavioral surrogates such as the Nociception Coma Scale and its revised version were developed to grade motor, verbal and facial responses to standardized noxious stimulation in patients with DoC and remain the clinical benchmark (125,126); however, they are inapplicable when motor output is abolished by sedation, neuromuscular blockade or brainstem injury. EEG provides a complementary, direct cortical read-out. In comatose intensive-care patients, standardized noxious stimulation elicits reactive changes in EEG background activity even in the absence of a behavioral response; in a prospective comparison of three noxious stimuli, bilateral nipple pinching was the most efficient trigger of EEG reactivity, whereas nailbed compression and nasal pinprick were less consistent (127). Since visual rating of such reactivity exhibits fair inter-rater agreement, subsequent work has moved towards quantifiable stimulation and quantitative EEG: Standardized median-nerve electrical stimulation combined with spectral-power quantification outperformed conventional pain stimulation with visual analysis for predicting good neurological outcome after cardiac arrest (area under the curve, 0.932 vs. 0.770) (128). In chronic DoC, laser-evoked potentials (LEPs) address the more specific question of residual nociceptive cortical processing: A δ - and C-fiber LEP components show longer latencies and lower amplitudes in unresponsive wakefulness syndrome than in the minimally conscious state and correlate with Coma Recovery Scale-Revised and Nociception Coma Scale-Revised scores (129,130), although LEPs may be preserved even in patients who are behaviorally unresponsive, so that their presence indicates nociceptive transmission rather than conscious pain experience (131). Objective electrophysiological monitoring therefore addresses precisely the population in which self-report and behavioral scales fail, but the current evidence rests on small, heterogeneous cohorts, is confounded by sedation, hypothermia and neuromuscular blockade and still lacks standardized acquisition protocols and validated thresholds; routine bedside use remains a goal rather than an established practice.

9. Clinical transformation and decision support

The clinical application of EEG biomarkers requires the establishment of an integrated monitoring and decision-making

framework applicable to diverse settings, including hospital wards, ICU and home environments. Portable wireless EEG devices can transmit data to the cloud in real time using WiFi or Long-Term Evolution (132-135). From the postoperative ward to the ICU, this system connects to bedside terminals to integrate vital signs, such as electrocardiography and blood pressure, to generate a pain risk report using a multi-parameter algorithm, while simultaneously displaying pain monitoring, sedation depth and respiratory fluctuations, thereby reducing diagnostic delays and improving the safety of acute pain management (36). Based on an automated early warning model, non-specialist medical staff can visually identify abnormal oscillations through light indicators on the interface and receive personalized recommendations, enabling timely adjustments to analgesic regimens or initiation of reassessment processes (136,137).

Based on dynamic monitoring, a closed-loop neuro-modulation platform can trigger interventions based on EEG markers. The system continuously tracks characteristics such as θ power, γ activity or α/β synchronization. When these exceed individualized thresholds (for example a sudden increase in θ - γ coupling or a sudden decrease in α waves), transcutaneous electrical nerve stimulation, SCS, DBS or vagus nerve stimulation is initiated, effectively 'closing the pain gate' at the level of the brain-spinal cord circuits, promoting the release of endogenous opioid peptides and achieving a real-time closed-loop from perception to inhibition (22,23). This model not only dynamically adjusts stimulation parameters based on immediate feedback but also optimizes threshold settings through machine learning to balance safety and efficacy. In the future, multicenter clinical trials are needed to further validate this closed-loop strategy and its long-term effectiveness across different pain subtypes and individual variations, promoting widespread implementation of this technology in real-world settings (121,138,139). To date and to the best of our knowledge, no closed-loop EEG-triggered analgesic system has been validated in controlled clinical trials.

10. Challenges and future directions

The present review synthesized and critically discussed the mechanistic framework of pain, EEG frequency and network characteristics, and the development of composite biomarker approaches. The present review also discussed potential future directions ranging from EEG feature-based approaches to AI-driven multimodal and closed-loop strategies. Although these advances provide a foundation for continued biomarker development, major barriers still prevent routine objective assessment or EEG-guided intervention. Three principal barriers currently limit clinical translation. First, a lack of standardization: Acquisition parameters, electrode configurations, preprocessing and feature definitions vary widely, precluding direct comparison; therefore, multicenter studies must reduce heterogeneity at the acquisition stage and apply harmonization methods to mitigate site effects (59). Second, individual variability: EEG signatures are strongly modulated by age, medication, arousal state and psychiatric comorbidity, limiting the transfer of group-level thresholds to individuals (59). Moreover, the construct validity of EEG-derived

features remains a challenge, as a number of neural signatures associated with pain may also reflect overlapping processes such as attention, arousal, emotional state or cognitive load. Third, limited large-scale validation: To date and to the best of our knowledge no single biomarker, EEG or otherwise, has achieved formal clinical validation for chronic pain, and current evidence does not support routine clinical implementation without large, prospective, multicenter studies using open, standardized datasets (140). Future efforts should focus on cross-center standardized protocols, low-channel wearable EEG for long-term monitoring, multimodal intelligent integration and closed-loop neural regulation trials to promote the implementation of precise, dynamic and personalized pain management.

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Availability of data and materials

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Authors' contributions

LZ conceived the review, conducted the systematic literature search, screened and selected the included studies and drafted the manuscript. NL and HW participated in literature screening and wrote and revised the manuscript. JZ and HJ contributed to the interpretation of findings and provided critical revisions to the manuscript. SD constructed figures and wrote and revised the manuscript. SY, HS and XC supervised the entire project, provided overall direction and revised the manuscript for intellectual content. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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