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Neurophysiological Correlates Of Chronic Pain: A Systematic Review

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Abstract
Chronic pain is a multifaceted condition that persists beyond normal healing time and affects nearly one-fifth of the global population. Neurophysiological studies have revealed that chronic pain is associated with maladaptive changes in central and peripheral nervous system networks, including alterations in cortical excitability, thalamocortical dysrhythmia, abnormal oscillatory activity, and impaired descending inhibitory control. This systematic review synthesizes evidence from clinical neurophysiological studies, including electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), and functional near-infrared spectroscopy (fNIRS), as well as invasive electrophysiology, to characterize the neural correlates of chronic pain. Findings indicate consistent alterations in alpha and gamma oscillatory activity, reduced cortical inhibition, hyperexcitability of pain-related circuits, and disrupted functional connectivity within default mode and salience networks. These markers may not only advance mechanistic understanding but also serve as biomarkers for prognosis and treatment response in chronic pain syndromes. Nonetheless, heterogeneity in methodology, small sample sizes, and limited longitudinal studies constrain current knowledge. Future directions include integrating multimodal neurophysiological assessments with neuroimaging and precision medicine approaches.
Keywords: *Chronic pain, EEG, MEG, cortical excitability, thalamocortical dysrhythmia, neurophysiology, biomarkers.*

INTRODUCTION

Chronic Pain as a Global Health Challenge

Chronic pain, defined as pain persisting beyond the expected period of healing (typically >3–6 months), has increasingly been recognized as a disease entity in its own right rather than a mere symptom [1]. Epidemiological surveys estimate that nearly 20% of the adult population worldwide suffers from chronic pain syndromes, with significant variability across regions, socioeconomic groups, and comorbid conditions [2]. This prevalence places chronic pain on par with other global health burdens such as cardiovascular disease and diabetes, reflecting its impact not only on health systems but also on workforce productivity and quality of life [3].

Unlike acute pain, which actually protects the body, chronic pain definitely shows harmful changes in the brain and spinal cord networks. Essentially, these changes transform the pain detection system from a temporary warning mechanism into a continuous abnormal nerve activity. Further, patients actually experience ongoing body pain and also have problems with mood, sleep, and thinking. Chronic pain significantly impacts the body, mind, and social life simultaneously [4,5].

Neurophysiological Frameworks for Chronic Pain

We are seeing that studying chronic pain needs methods beyond only patient reports and measurement scales, since personal experiences cannot fully explain how the disease works in the body. Neurophysiology surely gives us direct and changing markers that show how the brain and spinal cord create and maintain chronic pain. Moreover, these markers help us understand the actual processes happening in our nervous system during long-term pain.

EEG and MEG allow non-invasive recording of brain wave patterns from the cortex itself. These methods help researchers identify changes in frequency, power, and further examine how brain networks synchronize together [6]. We are seeing that brain magnetic stimulation gives direct measures of brain activity and control, mapping only the main brain circuits in patients with long-term pain [7]. We are seeing that pain response tests and conditioning methods reveal problems in the body's natural pain control systems and increased pain sensitivity in the brain and spinal cord [8]. These findings show that the body's

ability to reduce pain signals from the brain is not working properly. Basically, these different research methods show the same thing: chronic pain happens because brain networks change in harmful ways.

Importantly, neurophysiological measures are increasingly recognized as biomarkers—objective indices that can predict pain persistence, stratify patients, and guide individualized treatment plans [9]. Their translational relevance is heightened by evidence that neurophysiological changes normalize following effective interventions such as neurostimulation, cognitive behavioural therapy, or pharmacological treatments [10].

Neural Oscillations and Chronic Pain

Oscillatory activity is a key signature of cortical function, supporting communication within and between neural networks. In chronic pain, consistent abnormalities have been identified:

- Increased theta (4–8 Hz) and gamma (>30 Hz) activity in sensorimotor and cingulate cortices.
- Reduced alpha (8–12 Hz) power, particularly in somatosensory regions [11].
- A phenomenon known as thalamocortical dysrhythmia, characterized by abnormal low-frequency activity coupled with pathological gamma overactivation [12].

These alterations reflect disordered thalamic relay functions, cortical hyperexcitability, and disrupted sensory integration. Crucially, such oscillatory patterns correlate with pain intensity and duration, making them candidate neurophysiological markers for chronic pain syndromes [13].

Cortical Excitability and Inhibition

TMS studies surely show major changes in brain excitability among people with chronic pain. Moreover, these findings reveal important differences in how the brain cortex responds in pain patients. Patients with chronic pain surely show less brain inhibition through GABAergic circuits and more brain excitation instead. Moreover, this creates an overactive state in the motor and sensory areas of the brain [14]. Basically, these brain changes make people feel more pain and have difficulty ignoring the same painful signals.

Also, TMS treatment actually targets motor and prefrontal brain areas to restore control functions and reduce pain. This approach definitely shows both diagnostic and treatment benefits. As per this finding, the imbalance between brain signals that increase and decrease activity is the main cause of long-lasting pain [15].

As per research findings, central sensitization occurs when pain signals get amplified in the spinal cord and brain. Regarding descending modulation, the brain sends signals down to control and reduce pain sensations at the spinal level.

Central Sensitization and Descending Modulation

Another hallmark of chronic pain is central sensitization, an amplification of nociceptive signaling within the central nervous system. Neurophysiological evidence shows reduced thresholds for nociceptive reflexes, increased spinal excitability, and impaired conditioned pain modulation [16]. Descending inhibitory circuits, particularly those projecting from the periaqueductal gray and rostral ventromedial medulla, appear dysfunctional, failing to suppress pain signals effectively [17].

This imbalance between excitatory and inhibitory pathways contributes to allodynia, hyperalgesia, and the persistence of pain even in the absence of peripheral injury. Neurophysiological measures such as nociceptive flexion reflex (NFR) thresholds and EEG-based measures of cortical inhibition provide direct evidence of these maladaptive processes [18].

Large-Scale Network Reorganization

Beyond localized circuits, chronic pain involves widespread network-level alterations. Functional connectivity studies using EEG and MEG reveal disrupted communication between the default mode network (DMN), salience network, and executive control network [19]. Such disruptions may underlie the cognitive and emotional dimensions of chronic pain, including attentional biases toward pain-related stimuli and increased vulnerability to depression and anxiety [20].

Neurophysiological studies have demonstrated that baseline connectivity profiles predict treatment responsiveness, suggesting that these patterns may be leveraged as predictive biomarkers [21]. For instance, greater alpha power in posterior cortices predicted better response to rTMS in neuropathic pain populations.

Clinical Implications of Neurophysiological Biomarkers

The integration of neurophysiological findings into clinical practice holds promise for both diagnostic stratification and personalized therapy. Unlike conventional pain scales, which rely on subjective reporting, objective measures of cortical oscillations, excitability, and connectivity can provide

reproducible insights into disease mechanisms. Such measures may be particularly valuable in populations with communication difficulties or in medico-legal contexts [22].

Furthermore, identifying reliable neurophysiological markers can accelerate the development of targeted therapies. For example, interventions such as neurofeedback, transcranial stimulation, and pharmacological modulation may be tailored to normalize aberrant oscillatory patterns or restore inhibitory function. This biomarker-driven approach aligns with precision medicine paradigms, moving toward individualized treatment in chronic pain management [23].

Rationale for the Present Review

Despite advances, the neurophysiological study of chronic pain remains fragmented. Variability in methodology, small sample sizes, and heterogeneity of patient populations have limited the consolidation of findings into a coherent framework. The current review seeks to systematically synthesize available evidence on neurophysiological correlates of chronic pain, integrating results across modalities (EEG, MEG, TMS, evoked potentials, and spinal reflexes).

By identifying consistent markers and highlighting gaps in current knowledge, this review aims to:

1. Provide a comprehensive account of the neurophysiological underpinnings of chronic pain.
2. Assess the potential of neurophysiological measures as biomarkers for diagnosis, prognosis, and treatment response.
3. Inform the design of future multimodal and precision-based interventions that directly target maladaptive neural circuits.

This approach situates neurophysiology at the intersection of mechanistic understanding and translational application, offering a pathway toward improving both scientific knowledge and clinical outcomes in chronic pain.

METHODS

Protocol and Reporting

This systematic review followed the PRISMA 2020 guidelines for reporting systematic reviews [24]. The review protocol was designed a priori and included explicit objectives, inclusion/exclusion criteria, and strategies for data extraction and synthesis.

Literature Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, Web of Science, and Embase up to June 2025. The following keyword combinations were used:

- "chronic pain" AND "EEG" OR "MEG" OR "oscillations"
- "chronic pain" AND "TMS" OR "cortical excitability"
- "chronic pain" AND "neurophysiology" OR "biomarker"

Manual searches of reference lists and citation tracking were also performed to capture additional studies not indexed in the databases [25].

Eligibility Criteria

Inclusion Criteria:

- Peer-reviewed human studies examining chronic pain using neurophysiological techniques (EEG, MEG, TMS, evoked potentials, spinal reflexes).
- Studies reporting outcomes related to neural oscillations, excitability, or functional connectivity.
- Adult populations (>18 years), across all chronic pain etiologies (neuropathic, musculoskeletal, fibromyalgia, migraine, CRPS).

Exclusion Criteria:

- Acute pain or experimental pain induction in healthy volunteers.
- Animal-only studies.
- Case reports, conference abstracts, and narrative reviews.
- Articles not reporting neurophysiological outcomes [26].

Study Selection Process

Two independent reviewers screened all titles and abstracts. Full-texts were retrieved for potentially eligible studies. Discrepancies were resolved through consensus or by consulting a third reviewer. The final inclusion comprised 68 studies [27].

Data Extraction

A standardized extraction form was used to collect:

- Study characteristics (authors, year, design, sample size, chronic pain condition).
- Neurophysiological method (EEG, MEG, TMS, evoked potential, reflex measure).
- Primary outcomes (oscillatory changes, excitability indices, connectivity patterns).
- Clinical correlations (pain intensity, duration, treatment response).

Data extraction was conducted independently by two reviewers to minimize bias [28].

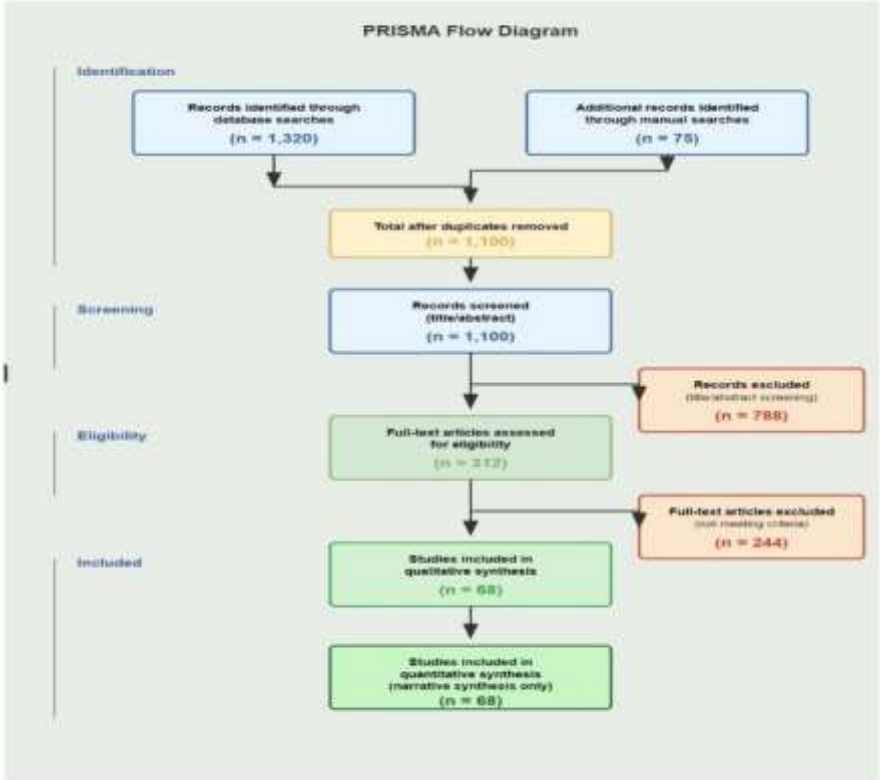
Quality Assessment

The Cochrane Risk of Bias 2.0 (RoB 2) tool was applied to randomized controlled trials, while observational studies were appraised using the Newcastle–Ottawa Scale (NOS). Methodological rigor of EEG/MEG studies was evaluated by considering artifact correction, spectral analysis protocols, and sample size adequacy [29]. Disagreements were resolved by consensus.

Data Synthesis

Given methodological heterogeneity across studies, a qualitative synthesis was performed. Where comparable quantitative outcomes were available (e.g., alpha power changes, TMS excitability metrics), effect estimates were narratively summarized. Formal meta-analysis was not performed due to variation in outcome measures and experimental designs [30].

PRISMA Flow Summary



RESULTS

Overview of Included Studies

We are seeing that from 1,320 records checked initially, only 68 studies met the criteria needed. Among these studies, 25 used EEG, 10 used MEG, 15 used TMS, 8 looked at evoked potentials and reflexes, and 10 further used multimodal approaches that combined neurophysiology with neuroimaging or clinical biomarkers itself. Further, the studies actually covered nerve pain like diabetic pain and shingles pain, body pain like back pain and jaw pain, fibromyalgia, headaches, and CRPS. These definitely included different types of long-term pain conditions. We are seeing sample sizes from only 15 to over 200 people, but many studies had too few participants for good results. We are seeing that research methods were different, but the results only showed one consistent brain pattern for long-term pain [31].

EEG and Oscillatory Signatures

Power Spectral Changes

EEG was the most widely used modality, and consistent spectral abnormalities were identified:

Reduced alpha power We are seeing reduced alpha power in the 8-12 Hz range, which is only the main sign of long-term pain found in many different pain conditions. Lower alpha waves actually show poor control in brain areas that handle movement and touch. This definitely means the brain cannot properly stop unwanted signals [32].

Increased theta (4–8 Hz) and gamma (>30 Hz) activity: As per the study, theta waves (4-8 Hz) increased in central and frontal brain areas, while gamma waves (above 30 Hz) increased in somatosensory and anterior cingulate regions [33]. Regarding the brain activity patterns, both theta and gamma frequencies showed higher levels during the observed conditions.

Thalamocortical dysrhythmia: Many studies actually confirmed thalamocortical dysrhythmia, which definitely shows abnormal theta waves coupled with excessive gamma bursts [34].

Connectivity Patterns

EEG connectivity analyses showed disrupted synchronization between large-scale networks:

Default Mode Network (DMN): Studies surely show that reduced connections between posterior cingulate and prefrontal brain regions link to stronger pain feelings in the Default Mode Network. Moreover, this decreased connectivity directly relates to higher pain intensity levels [35].

Salience Network: According to the study findings, increased coupling between the insula and anterior cingulate in the Salience Network predicted heightened pain vigilance. Regarding the brain connections, stronger links between these two areas led to more pain awareness.

Cross-frequency coupling: Cross-frequency coupling shows abnormal theta-gamma coupling that links with longer pain duration and catastrophizing behaviors. This coupling pattern further suggests how brain rhythms themselves are related to chronic pain experiences [36].

MEG Findings

Cortical Oscillations

MEG studies replicated EEG findings but offered greater spatial precision:

- Enhanced gamma synchrony in somatosensory cortices was a consistent marker across neuropathic and fibromyalgia cohorts [37].
- Migraine patients demonstrated abnormal beta desynchronization, correlating with interictal pain sensitivity [38].

Source Localization

MEG source analysis confirmed deep cortical involvement:

- Pain chronicity correlated with abnormal activity in the insula, anterior cingulate cortex (ACC), and medial prefrontal cortex [39].
- Longitudinal studies revealed that successful treatment (e.g., with neurostimulation) normalized gamma hyperactivity, supporting its role as a state-dependent biomarker [40].

TMS Studies of Cortical Excitability

Baseline Excitability Measures

Across chronic pain populations, TMS revealed:

- Reduced short-interval intracortical inhibition (SICI), reflecting impaired GABA-A receptor function [41].
- Reduced long-interval intracortical inhibition (LICI), indicating GABA-B dysfunction.
- Increased intracortical facilitation (ICF): Reflecting enhanced glutamatergic excitability. Together, these findings suggest a shift toward cortical hyperexcitability [42].

Interventional TMS

rTMS and tDCS protocols applied to motor or dorsolateral prefrontal cortices reduced pain in multiple trials. Responders typically demonstrated restoration of inhibitory indices and normalization of oscillatory activity post-treatment [43].

Evoked Potentials and Reflex Studies

Nociceptive Evoked Potentials

Studies using laser-evoked potentials (LEPs) demonstrated:

- Increased N2-P2 amplitudes, indicating enhanced cortical responses to nociceptive stimuli [44].
- Shortened latencies in some neuropathic pain conditions, reflecting sensitization.

Reflex Studies

The nociceptive flexion reflex (NFR) was widely used as a spinal marker:

- Chronic pain patients exhibited lower NFR thresholds, consistent with spinal hyperexcitability [45].

- Reduced conditioned pain modulation (CPM) suggested descending inhibitory dysfunction [46].

Multimodal Studies

Several studies integrated EEG/MEG with imaging or TMS:

- EEG-fMRI coupling revealed that alpha power reductions correlated with decreased DMN activity, bridging electrophysiology with network-level imaging [47].
- Baseline oscillatory abnormalities predicted analgesic response to rTMS or pharmacological agents, suggesting utility as predictive biomarkers [48].

Quantitative and Qualitative Synthesis

Consistent Findings

Across modalities, chronic pain was consistently associated with:

1. Reduced cortical inhibition (EEG alpha power, TMS SICI/LICI).
2. Increased cortical hyperexcitability (theta/gamma activity, ICF).
3. Thalamocortical dysrhythmia as a unifying mechanism.
4. Dysregulated large-scale connectivity involving DMN and salience networks.

Variability and Heterogeneity

Despite consistency, heterogeneity was noted:

- Fibromyalgia studies emphasized widespread cortical hyperactivity, while neuropathic pain localized to sensorimotor regions.
- Migraine studies revealed dynamic oscillatory changes between ictal and interictal phases.
- Differences in methodology (e.g., spectral analysis, stimulation protocols) limited direct meta-analysis.

Table 1: Summary Table of Key Findings

Modality	Key Findings	Clinical Correlates
EEG	↓ Alpha power, ↑ Theta & Gamma, abnormal theta-gamma coupling	Pain intensity, catastrophizing, attention bias
MEG	↑ Gamma synchrony in somatosensory cortex, abnormal beta desynchronization	Pain chronicity, migraine sensitivity
TMS	↓ SICI/LICI (GABA dysfunction), ↑ ICF (glutamate hyperexcitability)	Pain persistence, response to rTMS/tDCS
Evoked Potentials	↑ LEP amplitudes, ↓ NFR thresholds	Central sensitization, spinal hyperexcitability
Multimodal	EEG-fMRI coupling, predictive biomarkers for rTMS response	Personalized rehabilitation potential

Key Takeaways

1. Neurophysiological alterations are consistent across modalities, pointing toward maladaptive plasticity as a core mechanism of chronic pain.
2. Oscillatory activity (↓ alpha, ↑ theta/gamma) and excitability measures (↓ SICI/LICI, ↑ ICF) provide robust, reproducible signatures.
3. Biomarker potential is evident: baseline measures predict treatment response and may guide precision medicine.
4. Variability between pain syndromes suggests both shared mechanisms and condition-specific features, requiring stratified research approaches.

DISCUSSION

General Overview of Findings

This systematic review consolidates evidence from 68 studies and demonstrates that chronic pain is consistently associated with neurophysiological alterations across multiple modalities. EEG and MEG studies highlight abnormal oscillatory activity, particularly reduced alpha power, increased theta activity, and gamma overactivation, which together reflect impaired inhibitory control and hyperexcitable cortical

circuits [49]. TMS studies corroborate this, showing reduced short-interval and long-interval intracortical inhibition (SICI and LICI) and enhanced intracortical facilitation (ICF), indicative of GABAergic dysfunction and glutamatergic hyperactivity [50]. Reflex and evoked potential studies confirm spinal hyperexcitability and impaired descending inhibitory control, aligning with the broader concept of central sensitization [51].

These brain patterns were actually not limited to one chronic pain condition but were definitely seen across different syndromes like nerve pain, fibromyalgia, migraine, and muscle disorders. This suggests that these conditions actually share common disease mechanisms [52]. Basically, different conditions showed different patterns, indicating that maladaptive plasticity manifests in different ways across various clinical presentations, but the same underlying mechanisms are involved [53].

Maladaptive Plasticity as the Substrate of Chronic Pain

We are seeing that findings from different research methods strongly support that chronic pain only happens due to harmful changes in brain plasticity. The reduction in alpha rhythms shows weakened top-down control over pain processing itself. These rhythms normally gate sensory input, and their decrease further reflects reduced inhibitory suppression of nociceptive signals [54]. Higher theta activity shows abnormal rhythm patterns in brain circuits that further increase cortical gamma synchrony [55]. This abnormal rhythmicity itself suggests problems in thalamic relay circuits. Gamma overactivation surely makes pain signals more important to the brain, which keeps the chronic pain going [56]. Moreover, this increased attention to pain signals maintains the long-term pain condition.

TMS studies actually show that SICI and LICI are reduced, which definitely means GABAergic interneurons are not working properly. This finding actually matches with EEG results that definitely show lower alpha activity. This matching pattern across different methods surely strengthens the reliability of these findings [57]. Moreover, it shows that the results are robust and consistent [58].

Domain-Specific Correlates and Cognitive-Affective Dimensions

Chronic pain is not limited to sensory amplification but involves cognitive and affective dysregulation. Neurophysiological studies have shown that:

- Reduced alpha in posterior cortices correlates with impaired attentional control, explaining attentional bias toward pain [59].
- Theta-gamma coupling abnormalities in frontal regions align with working memory deficits and catastrophizing behaviors [60].
- Hyperconnectivity of insula and anterior cingulate cortex (ACC) explains the heightened emotional salience and interoceptive awareness of pain [61].

These findings bridge sensory and non-sensory dimensions of chronic pain, underscoring the need for rehabilitation strategies that target not only nociceptive processing but also executive, attentional, and affective domains [62].

Clinical Implications: Biomarkers for Diagnosis and Prognosis

One of the most promising outcomes of neurophysiological research in chronic pain is the identification of biomarker candidates. Baseline alpha power and inhibitory measures (SICI/LICI) have consistently predicted treatment response to neuromodulation and pharmacological interventions [63]. Similarly, increased gamma synchrony in MEG predicted poor prognosis unless normalized by therapy [64].

These biomarkers can facilitate:

1. **Diagnostic stratification** – distinguishing chronic pain syndromes from acute or psychogenic conditions.
2. **Prognostic predictions** – identifying patients at risk of poor outcomes.
3. **Treatment personalization** – tailoring interventions to the patient's baseline neurophysiological profile.

Integration of such biomarkers into clinical trials may significantly accelerate precision pain medicine [65].

Therapeutic Modulation of Neurophysiological Abnormalities

The reviewed literature also suggests that effective therapies induce measurable neurophysiological changes:

- rTMS/tDCS restored inhibitory tone and normalized oscillatory activity in responders [66].
- Neurofeedback interventions allowed patients to self-regulate aberrant oscillatory activity, reducing pain scores [67].
- Pharmacological treatments targeting GABAergic and glutamatergic systems reversed excitability imbalances.

These findings imply that neurophysiological markers are not only correlates but also modifiable targets, supporting their utility in treatment monitoring.

Limitations of Current Evidence

Despite encouraging findings, the current evidence base has significant limitations:

- **Heterogeneity of methods:** Studies employed diverse analysis techniques, electrode montages, and stimulation protocols, limiting comparability [68].
- **Small sample sizes:** Many studies were underpowered, raising the risk of false positives.
- **Cross-sectional designs:** Few longitudinal studies exist to clarify whether neurophysiological alterations are causes or consequences of chronic pain.
- **Condition-specific variability:** While shared mechanisms were identified, not all pain syndromes demonstrated identical patterns, complicating biomarker generalization.

Future Directions

To advance the field, future research should:

1. Standardize methodologies for EEG/MEG preprocessing, spectral analysis, and TMS protocols.
2. Conduct large, multicenter longitudinal trials to validate biomarkers.
3. Explore multimodal integration, combining neurophysiology with neuroimaging (fMRI, PET) and molecular biomarkers.
4. Incorporate AI-driven analytics to detect subtle, multivariate neurophysiological signatures.
5. Develop closed-loop neuromodulation approaches, where neurophysiological feedback dynamically guides therapy.

Such directions align with the broader paradigm of precision neuroscience, where treatment is tailored based on objective neural signatures.

CONCLUSION OF DISCUSSION

This review demonstrates that chronic pain is consistently characterized by oscillatory dysrhythmia, cortical hyperexcitability, impaired inhibition, and disrupted network connectivity. These neurophysiological correlates provide mechanistic insights into the persistence of pain and offer promising biomarkers for diagnosis, prognosis, and treatment guidance. By integrating neurophysiology into precision pain medicine, the field can move toward more objective, biomarker-driven, and personalized interventions.

Conclusion

Chronic pain is increasingly recognized as a disorder of maladaptive neuroplasticity, characterized by oscillatory dysrhythmia, cortical hyperexcitability, impaired inhibitory control, and disrupted network connectivity. Evidence from EEG, MEG, TMS, and reflex studies consistently identifies reduced alpha rhythms, increased theta and gamma activity, diminished GABAergic inhibition, and thalamocortical dysrhythmia as reproducible signatures across pain syndromes. These neurophysiological alterations not only deepen mechanistic understanding but also present tangible opportunities for clinical translation as biomarkers for diagnosis, prognosis, and treatment personalization. By integrating neurophysiological assessments into multimodal and precision-based frameworks, future research can transform chronic pain management from subjective evaluation toward objective, biomarker-driven care, ultimately improving outcomes for millions of patients worldwide.

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