

Review

## Advancing Objective Pain Measurement: Exploring the Potential of Electroencephalography Biomarkers

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### Abstract

Chronic pain involves complex cortical and subcortical changes, suggesting that brain electrical activity may be a potential biomarker for nociceptive processing. Pain leaves its signature in the brain's oscillatory patterns, yet limited studies have explored the neurophysiological alterations associated with chronic pain. This review examines the pain detection method currently used in clinical settings, the potential of neurophysiological features to become brain oscillatory brain biomarkers, and their use in future medical advances.

### Keywords

Brain oscillations; electroencephalography (EEG); pain; computational neuroscience



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## 1. Introduction of Pain

As the International Association for the Study of Pain (IASP) noted in 2020, it reads: "An unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage." This definition conveys the implicit understanding that pain has sensory and affective elements, both nociceptive (the physiological encoding and processing of noxious stimuli) and neuropathic (pain occurring without the presentation of stimuli), as well as cognitive elements. IASP has revised the definition notes, noting that pain is "Verbal description is only one of several behaviours to express pain." Pain can be broadly categorized into three main types: nociceptive, neuropathic, and nociplastic. Nociceptive pain, including its inflammatory subtype, is typically associated with acute injury or tissue damage, such as a torn muscle or sprained ankle, where pain arises from the activation of peripheral nociceptors. Neuropathic pain, on the other hand, results from damage or dysfunction within the somatosensory nervous system itself, leading to abnormal signal processing. A third category, nociplastic pain, refers to pain that emerges from altered nociceptive function without clear evidence of actual or threatened tissue damage or identifiable lesions in the nervous system. This type of pain is believed to be driven by dysregulation in pain processing pathways rather than structural injury (IASP).

Pain serves as a crucial protective signal, alerting the body to actual or potential tissue damage and requiring brain interpretation to initiate an appropriate response. A wide range of chemical, thermal, inflammatory, and mechanical stimuli can trigger acute pain by activating nociceptive pathways. Substances such as prostaglandins, bradykinin, serotonin, substance P, and histamine activate nociceptors, triggering the initiation of action potentials. These signals are carried from the periphery to the brain through a multi-step process: transduction of noxious stimuli, transmission to the spinal cord, brainstem, and thalamus, and finally to the cerebral cortex for pain processing [1]. The thalamus plays a crucial role in integrating sensory information before projecting it to higher brain regions for the perception of pain. This complex process is dynamically influenced by both sensory input and individual cognitive-emotional factors [2].

Acute pain can progress into chronic pain, which is not merely a temporal extension of the acute phase. Instead, it involves complex neural plasticity within pain circuits, leading to adaptive changes at the cellular, molecular, structural, and functional levels. These alterations contribute to shifts in pain perception and the development of compensatory behavioral responses [3]. Macroscopic brain imaging studies in both humans and animal models have revealed maladaptive plasticity within the brain's 'pain matrix,' contributing to the development and maintenance of chronic pain. Notably, the primary somatosensory cortex (S1) provides key insights into the functional and structural changes in neurons, glial cells, and synapses associated with chronic pain [4].

Tissue or nerve injury can induce widespread plastic changes across the peripheral nervous system, spinal cord, and brain, ultimately altering pain perception and contributing to chronic pain. At the cellular level, such injuries activate both the innate and adaptive immune responses, initiating inflammation that, if unregulated, can lead to neuropathic pain [5]. Abnormal amplification of signals occurs within the pain transmission circuitry, such as the spinal cord or supraspinal structures, without the presence of an external stimulus or injury. Accumulating evidence highlights the role of the anterior cingulate cortex (ACC) in the affective dimension of pain processing, including neuropathic pain, where synaptic proteins in the ACC are known to modulate synaptic plasticity, thereby contributing to the development and maintenance of neuropathic pain [6].

Structural and functional reorganization occurs throughout the central nervous system, including the cortex, thalamus, brainstem, and spinal cord. Synaptic activity, modulated by nociceptive input and neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), regulates protein synthesis, turnover, and signal transmission, driving dynamic changes within neural networks [7]. Notwithstanding its protective function, peripheral nerve injury can elevate extracellular glutamate levels in the primary somatosensory cortex, primarily due to increased excitation of thalamic neurons and their cortical projections. This glutamatergic surge reactivates the mGluR5–Ca<sup>2+</sup>–TSP-1 signaling cascade in somatosensory astrocytes, leading to synaptic remodeling, including increased synaptogenesis, synaptic pruning, and strengthening of persistent synapses. These changes can lead to local hyperexcitability of the cortex in response to peripheral input. This heightened excitability may also influence other pain-related cortical regions, such as the anterior cingulate cortex (ACC), ultimately contributing to the transition from acute to chronic pain [7]. These adaptive and sometimes maladaptive processes are supported by macroscopic brain imaging findings that show plastic alterations in key pain-related regions collectively known as the 'pain matrix'.

Pain can be considered chronic if it persists beyond the normal healing time, hence lacking the acute warning function of physiological nociception. Typically, pain is considered chronic when it persists or recurs for three to six months or longer. It is estimated that pain affects 20 percent of people worldwide. This global suffering is categorized into several groups based on its etiology and characteristics. Chronic primary pain involves one or more body regions with significant emotional or functional impact and no clear underlying condition, including disorders like fibromyalgia and nonspecific back pain. Chronic cancer pain results from cancer itself or its treatments and includes visceral, bony, and neuropathic components. Chronic postsurgical and posttraumatic pain develops after surgery or injury and often has a neuropathic component. Chronic neuropathic pain arises from lesions or diseases of the somatosensory nervous system and requires clinical and diagnostic confirmation. Chronic headache and orofacial pain, occurring on at least 50% of days over three months, includes migraines, tension-type headaches, and temporomandibular disorders. Chronic visceral pain originates from internal organs, often presenting as referred pain due to shared sensory pathways, and may involve mechanisms such as inflammation or obstruction. Chronic musculoskeletal pain is typically nociceptive in origin, associated with conditions affecting bones, joints, muscles, or soft tissues, such as arthritis and osteoarthritis. Other pain types affecting musculoskeletal regions are categorized separately. This classification framework guides diagnosis and management of persistent pain across clinical contexts [8].

## **2. Current Pain Detection System**

Pain is perceived as an unpleasant sensory and emotional experience linked to actual or potential tissue damage [9]. Pain severity, classified as mild, moderate, or severe, is currently being assessed using different approaches, including self-reporting, behavioural cues (e.g., vocalizations, facial expressions, body movements), and physiological activity. Self-reported measures are considered the gold standard in clinical pain assessment. Tools like the Numerical Rating Scale (NRS) and Visual Analog Scale (VAS) offer a quick, simple, and effective way for patients to communicate their pain levels, making them easy for both patients and clinicians to use. However, these tools depend on the patient's ability to assess and express their pain. For individuals who struggle with numerical

scales, such as young children, individuals with speech impairments, or those with learning disabilities, the Verbal Rating Scale (VRS) provides an alternative by using descriptive words instead of numbers. However, VRS has limitations where it may be ambiguous, making it difficult for patients to choose the most accurate description of their pain. Additionally, language barriers can affect the effectiveness of VRS in pain assessment [10]. Furthermore, pain is uniquely personal and subjective to different individuals, causing difficulty and unstandardisation in assessing its severity and intensity [11]. Therefore, accurate and timely pain evaluation is essential for effective pain management and better patient outcomes. If left unmanaged, pain can induce physiological stress, exacerbate medical conditions, and impair overall well-being. Several pain assessment scales are commonly used in clinical settings to evaluate pain severity level. These standardized healthcare professionals accurately measure pain intensity, monitor its progression, and guide treatment decisions. The most widely used pain detection scales include:

### **2.1 Wong-Baker Face Pain Rating Scale (WBFPS)**

The Wong-Baker Faces Pain Rating Scale (FPS) is a pain assessment tool that uses facial expressions to represent varying levels of pain intensity, combining pictures and numerical ratings to assess pain levels. This scale consists of six distinct facial expressions, ranging from a happy face (no pain) to a highly distressed face (severe pain), with scores assigned on a scale of 0 to 10. Initially developed for children aged three and above, the FPS helps young patients visually express their pain by selecting the face that best represents their discomfort. Each facial expression corresponds to a specific pain score: 0 ("No hurt"), 2 ("Hurts a little bit"), 4 ("Hurts a little more"), 6 ("Hurts even more"), 8 ("Hurts a whole lot"), and 10 ("Hurts worst"). The simplicity and visual nature of this scale make it particularly useful for pediatric patients, as well as individuals who may struggle with verbal pain assessment [12]. The FPS is inherently subjective since the scales rely on facial expressions to depict pain intensity. Although the faces are designed to represent a spectrum of pain levels, variations in individual pain perception can lead to inconsistencies in how patients select the expression that best reflects their discomfort [11].

### **2.2 Comfort Scale**

The COMFORT Scale, developed by Ambuel in 1992, is a validated tool used to assess pain levels in critically ill patients, particularly in children under 18 years of age and elderly individuals who are sedated or uncommunicative. This scale incorporates both physiological and behavioural indicators to evaluate a patient's pain and distress levels. Assessing pain in unconscious or non-communicative patients is challenging, as self-reported pain descriptions are typically crucial for accurate assessment. In such cases, the COMFORT Scale serves as a reliable alternative. It includes multiple parameters, each rated on a scale from 1 to 5, resulting in a total score ranging from 9 to 45. This structured approach provides a comprehensive evaluation of pain and discomfort, aiding healthcare providers in making informed decisions about pain management [13].

COMFORT scale uses non-verbal indicators in assessing pain, particularly for patients who are unable to communicate verbally due to sedation, unconsciousness, or cognitive impairment. The parameters include alertness, calmness/agitation, respiratory response (especially for intubated and ventilated patients), physical movement, muscle tone, and facial muscle activity.

- **Alertness:** Patients exhibit varying levels of consciousness, ranging from deep sleep (eyes closed, unresponsive to environmental changes) to light sleep, drowsiness, wakefulness, or hyper-alertness. These stages provide insight into the patient's responsiveness and neurological state.
- **Calmness/Agitation:** Calmness and agitation are key psychological indicators in pain assessment, reflecting the patient's emotional state and potential distress. The spectrum ranges from a calm and composed state to mild anxiety, increasing restlessness, and extreme panic. Agitation can serve as an indirect marker of pain or discomfort, particularly in patients who struggle with verbal communication. Theoretical perspectives suggest that agitation may arise when caregivers are unable to effectively interpret the patient's needs, leading to heightened anxiety and frustration due to the individual's inability to express their discomfort or personal requirements [14].
- **Respiratory Response** (for Intubated and Ventilated Patients): The patient's breathing patterns and vocal responses provide critical pain-related cues. These responses range from quiet breathing (with no crying or sound) to occasional sobbing or moaning, whining with monotonous vocalization, and extreme distress marked by screaming or shrieking.
- **Physical Movement:** The extent of body movement can indicate pain intensity. This ranges from no movement at all, occasional slight movements (three or fewer), frequent slight movements (more than three), vigorous movement confined to extremities, to full-body, uncontrolled movements involving the torso and head.
- **Muscle Tone:** Pain often influences muscle tone, which can be completely relaxed (no muscle tension), reduced (lower than usual), normal, increased (flexion of fingers and toes), or extreme muscle rigidity (with pronounced flexion of fingers and toes). Increased muscle tension may be a physiological response to pain.
- **Facial Muscle Activity:** Facial expressions are a well-established indicator of pain. The spectrum includes a relaxed face with no tension, normal muscle tone, slight tension in some muscles (not sustained), sustained tension throughout facial muscles, and extreme grimacing or contorted facial expressions [15].

Pain assessment based solely on observable behaviour has limitations. Therefore, nurses should use the Visual Analog Scale (VAS) in conjunction with the COMFORT Behaviour Scale for a more comprehensive evaluation. The VAS score reflects the nurse's expertise and understanding of the patient's pain intensity [16].

### 2.3 McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) and its shorter version, the Short Form MPQ (SF-MPQ), are globally recognised and reliable tools for multidimensional pain assessment in both clinical and experimental studies [17]. Pain is a complex experience encompassing sensory, affective-motivational, and cognitive components, prompting the development of comprehensive tools like the MPQ [18]. The MPQ and SF-MPQ are widely used for quantitative pain assessment in acute and chronic conditions, including musculoskeletal, post-surgical, and neuropathic pain. The SF-MPQ is particularly effective in detecting subtle changes in pain intensity. Unlike the Visual Analog Scale (VAS), which relies on the patient's cognitive, sensory, and motor abilities, the SF-MPQ provides a

more accurate measure of pain, avoiding the underestimation that may occur with VAS due to these cognitive demands [19].

## **2.4 VAS**

The Visual Analog Scale (VAS) is a widely used and validated pain assessment tool [20], utilizing a 100-mm scale that ranges from 0 (no pain) to 10 (the worst imaginable pain). Its simple administration and scoring make it highly user-friendly for patients. Pain scores from a horizontal VAS follow a normal distribution, unlike vertical VAS. Additionally, reading patterns may influence the preferred orientation [11]. VAS is considered more precise than NRS, which measures pain in millimetres rather than whole numbers, providing greater detail. This methodological difference contributes to the lower reproducibility of NRS, while VAS is age-sensitive and evaluates pain as a complex experience, whereas NRS solely focuses on current pain intensity. Despite this, VAS has notable limitations, as it requires patients to translate abstract sensory experiences into a linear representation, which makes it challenging for specific individuals to rate it precisely. This scale also exhibits a ceiling effect, making it difficult to discern a high level of pain [21]. Despite that, unlike the Numeric Rating Scale (NRS) or Verbal Rating Scale (VRS), the VAS depends on visual acuity, limiting its usability for patients with visual impairments.

## **2.5 Numerical Rating Scale**

The Numeric Rating Scale (NRS) is a widely used and reliable tool for pain assessment. The most common version is the 11-point scale, ranging from 0 (no pain) to 10 (the worst pain imaginable) [22]. Patients are asked to select the number that best reflects their pain intensity, with scores ranging from 1 to 3 indicating mild pain, 4 to 6 indicating moderate pain, and 7 to 10 indicating severe pain. Due to its simplicity, quick administration, and minimal translation issues, the NRS is the preferred tool for evaluating pain. However, some patients may struggle to express their pain accurately within a fixed numerical scale, particularly those with cognitive impairments or limited numerical literacy, as the NRS lacks visual or descriptive cues beyond the endpoints [23].

## **2.6 Verbal Rating Scale**

The Verbal Rating Scale (VRS), or the Verbal Descriptor Scale (VDS), uses 4 to 15 descriptive terms to represent pain intensity, indicating non-mild-moderate-severe pain. This is simple and widely preferred, especially by elderly patients, as they are asked to choose the descriptor that best reflects their pain level [23]. However, its ordinal nature limits statistical analysis to non-parametric methods, reducing sensitivity in detecting treatment effects. The scale's effectiveness also depends on the number of descriptors used, where 11 descriptors are as sensitive as the VAS, while fewer than five may lack responsiveness. Additionally, VRS relies on patients' literacy, as they may inaccurately interpret it, and the fixed set of terms may not fully capture a patient's pain experience, making it challenging for some individuals to find an option that precisely represents their pain intensity or quality.

This highlights the increasing need for objective, neurophysiological methods to detect and assess pain. Despite advancements, pain still lacks widely accepted clinical biomarkers. While some existing markers are intended to supplement self-reports by indicating pain intensity, others aim to

uncover the underlying pathophysiological mechanisms that cause pain [24]. To address this gap, neuroimaging techniques such as functional MRI (fMRI), electroencephalography (EEG), and positron emission tomography (PET) have been increasingly investigated for their potential to identify reliable biological markers linked to pain perception and processing. These modalities provide more accurate and objective means to measure neural activity, structural changes, and biochemical processes associated with pain. By detecting specific brain patterns or responses related to pain, these neuroimaging techniques provide valuable insights into pain mechanisms, enabling the development of more effective and individualized pain management strategies [25].

For instance, functional Magnetic Resonance Imaging (fMRI) is widely used to examine functional changes in the central nervous system in response to pain. It measures brain activity indirectly through blood oxygen level-dependent (BOLD) signals, reflecting regional blood oxygenation following neuronal activation. Brain regions include the anterior insula, anterior cingulate cortex, somatosensory cortices, prefrontal cortex, and posterior parietal cortex reported to be involved in pain processing. Subcortical structures, such as the periaqueductal gray, hypothalamus, amygdala, hippocampus, and cerebellum, also play crucial roles. The 'dynamic pain connectome' highlights the imbalance in functional brain networks as the cause of chronic pain. This alteration in network connectivity, particularly in the default mode and salience networks, was indicative of pain severity, and distinguishing pain-specific neural responses from other salient sensory stimuli remains challenging due to central sensitization. Similar brain activity patterns have been observed in individuals with and without pain sensitivity, raising concerns about the specificity of neuroimaging for pain assessment. Additionally, the low temporal resolution of fMRI limits its ability to capture rapid neural dynamics, restricting its clinical applicability [26].

Sole reliance on single modality may not provide a comprehensive assessment of pain. Integrating additional modalities, such as electromyography (EMG) and facial expression analysis, could significantly enhance the accuracy and robustness of pain evaluation. A multimodal approach is particularly valuable in capturing the complex and multidimensional nature of pain. EMG, for example, provides complementary insights by detecting peripheral muscle responses associated with sensory processing. Although EMG does not measure pain directly, it reflects muscle activity such as facial movements that often correlates with pain-related expressions. EEG studies have consistently shown that painful stimuli elicit reliable N2-P2 complex waveforms and gamma-band oscillations, albeit with considerable variability depending on stimulus characteristics. Concurrently, facial EMG signals, especially from the zygomaticus muscle, exhibit significant modulation corresponding to subjective pain ratings. Notably, a combined analysis using a general linear model demonstrated that both EEG-derived N2-P2 components and EMG responses from facial muscles significantly contribute to pain prediction. These findings underscore the potential of multimodal neurophysiological approaches to advance objective and real-time pain assessment [27].

Recent advancements in human neuroimaging also made it possible to investigate the functional connectivity between different brain regions involved in pain processing. However, numerous studies have mapped pain-related activity with high anatomical precision, the precise neural signals that mark the timing of pain onset remain poorly understood. Uncovering when pain signals emerge within distributed cortical networks could shed light on the temporal dynamics of pain perception and offer critical insights for developing real-time, closed-loop neuromodulation strategies for pain management [28]. Electroencephalography (EEG), a non-invasive neuroimaging technique, offers several key advantages for clinical use over other imaging modalities.

Most notably, it provides excellent temporal resolution, enabling the real-time monitoring of brain oscillatory activity associated with pain processing [2]. Research has demonstrated that acute pain elicits distinct EEG patterns, including event-related potentials (ERPs) and increased low frequency components and alpha event-related desynchronisation and theta and gamma band power [29] and overactivation from the qEEG source localisation [30]. At the same time, chronic pain is often characterized by alterations in brain oscillatory frequencies. EEG records the brain's electrical activity, and pattern analysis helps detect neural activation related to pain at specific frequencies. Spectral analysis breaks down EEG signals into frequency components, which can be divided into five bands, ranging from the slowest to the fastest: delta, theta, alpha, beta, and gamma. EEG offers high temporal resolution, making it particularly suited for studying dynamic processes such as pain perception [31]. Examining brain oscillatory activity has revealed neural signatures associated with pain, such as altered power spectral density and connectivity patterns [32].

### **3. Revisiting the Neurophysiology of Pain**

The brain is composed of highly interconnected neural elements, organized into large networks that are spatially distributed yet highly integrated. These modules interact to form a system of networks within networks, ensuring efficient global communication and collaboration. Upon receiving input, active nodes broadcast information across the network. When all nodes are active, this communication can propagate throughout the entire brain network. Such activation occurs in two forms: synchronization and desynchronization. For instance, desynchronization alpha band oscillations with smaller amplitudes, which are characteristic of activated cortical regions, serve as electrophysiological correlates of cortical activation. In contrast, synchronized alpha oscillations are typically associated with resting or idling states, where little information flow occurs [33].

When tissues are injured or inflamed, sensory nerve endings release chemical mediators such as prostaglandins, bradykinin, and substance P, which heighten pain sensitivity. These pain signals travel through peripheral nerves to the spinal cord and brain, where they are processed and interpreted as pain [34]. In the spinal cord, pain signals are regulated by excitatory neurotransmitters (e.g., glutamate, substance P) that amplify pain and inhibitory neurotransmitters (e.g., GABA, endogenous opioids) that suppress it. The dorsal horn serves as a key relay centre in this process. Persistent pain can alter these pathways, leading to central sensitization, where the nervous system becomes overly sensitive to pain stimuli [35]. Central sensitization increases neuronal excitability, disrupts synaptic function, and weakens pain inhibition, heightening pain perception and reducing tolerance [36]. Excessive spinal neuron activation, driven by NMDAR and reduced inhibitory neurotransmitters (Gly, GABA), amplifies pain signals, creating a cycle of worsening pain, fatigue, and other symptoms [37].

The dynamic interactions between sensory and contextual processes, including cognition, emotion, and motivation regarding pain, produce alterations in the neuronal oscillatory rhythms, making pain perception closely tied to neuronal oscillations and synchronization across multiple frequencies, ranging from 0.1 to 100 Hz (delta, theta, alpha, beta, and gamma) rhythms [2]. These oscillatory patterns reflect complex neural interactions in the brain's pain-processing network, which encompasses the somatosensory cortex, insular cortex, cingulate cortex, prefrontal cortex, thalamus, subcortical structures, and brainstem [38]. Electroencephalography (EEG) and Magnetoencephalography (MEG) studies have revealed that noxious stimuli provoke a complex

spectral-temporal-spatial pattern of neuronal responses. Notably, pain induces an increase in slow-wave oscillations, particularly in the delta and theta bands. These rhythms are thought to originate from regions like the sensorimotor cortex, frontoparietal operculum, insular cortex, secondary somatosensory cortex, and mid-anterior cingulate cortex [39]. This rich and intricate neural response provides insights into the brain's pain-processing mechanisms, emphasizing the potential of neurophysiological biomarkers, such as EEG, to offer objective, precise, and reproducible measures of pain that cannot be influenced by subjective interpretation.

#### **4. EEG as a Neurophysiological Tool for Pain Assessment**

EEG is a non-invasive neurophysiological technique used to measure the brain's electrical activity, primarily generated by the synchronous postsynaptic potentials of cortical pyramidal neurons. These voltage fluctuations are detected at the scalp via surface electrodes and arise from excitatory and inhibitory inputs across large neural populations. At the cellular level, the neuronal membrane maintains a resting potential of approximately  $-70$  mV through the selective permeability of ions and active transport mechanisms. Voltage-gated ion channels modulate this potential during stimulation, leading to depolarization, repolarization, or hyperpolarization, electrical events that underlie the generation and propagation of action and synaptic potentials, and form the basis of the EEG signal [40].

##### **4.1 An Overview of EEG Methodology at a Glance**

Participant selection is a crucial first step in the early stage of EEG pipeline research, ensuring dataset homogeneity despite the inherent inter-individual variability in EEG signals. To maintain consistency, strict inclusion and exclusion criteria are applied, for instance, age, gender, and handedness. To minimize confounding factors and ensure the health status of participants, individuals who are pregnant or have chronic medical conditions, psychiatric disorders, or neurological impairments are commonly excluded. This careful screening process helps to enhance the reliability and interpretability of EEG data by reducing variability due to non-neural influences [41].

Electrodes are placed according to the International 10–20 system, a widely accepted standard for consistent electrode positioning based on anatomical landmarks. Electrodes labeled F, T, P, O, and C correspond to the frontal, temporal, parietal, occipital, and central regions of the brain, respectively. Odd numbers denote the left hemisphere, even numbers the right, and the letter 'z' represents midline sites. The '10' and '20' refer to electrode spacing based on 10% or 20% of the total front-back or lateral distance of the skull. Before electrode placement, the scalp was prepared to reduce impedance below  $50$  k $\Omega$ , as higher impedance can degrade data quality. Scalp factors, such as hair length, thickness, cleanliness, and skin texture, were considered to ensure optimal contact. Additionally, electrodes were not placed over moles, scars, or broken skin [42].

The raw EEG signals will be filtered using a bandpass filter to eliminate low-frequency drifts and high-frequency noise. A notch filter at  $50$  Hz is applied to remove electrical interference from power lines. Data preprocessing included Independent Component Analysis (ICA) to identify and remove physiological artifacts such as eye blinks, muscle activity, and heartbeat. Additional artifact rejection is performed based on statistical measures, such as variance and kurtosis. Clean EEG epochs are

extracted and time-locked to stimuli or events, typically in the range of –200 to +800 milliseconds for event-related potential (ERP) analysis [43].

G.Tec Medical Engineering GmbH (Austria), founded by Dr. Christopher Guger, is internationally recognized for its development of advanced neurophysiological recording systems, particularly high-fidelity EEG amplifiers. Their devices include the Unicorn Hybrid, and Nautilus is engineered to deliver high signal precision with ultra-low noise levels, thereby optimizing the signal-to-noise ratio (SNR) that is crucial for capturing subtle neural oscillations. These systems are extensively utilized in cognitive neuroscience, brain-computer interface (BCI) research, clinical neurodiagnostics, and neuromodulation studies. G.Tec's EEG amplifiers support high sampling rates (up to 38.4 kHz) and multi-channel configurations (up to 256 channels), allowing for fine-grained spatial and temporal resolution of cortical activity. Furthermore, their systems are designed to be compatible with real-time data processing frameworks and integrate seamlessly with signal preprocessing pipelines, including artifact removal (e.g., ICA for EOG/EMG correction), bandpass filtering, and epoching. Due to their robustness, modularity, and compliance with clinical-grade standards (CE, FDA), they are suitable for use in clinical settings. Tec devices are widely adopted in both experimental research and translational clinical applications, including EEG-based biomarkers, epilepsy monitoring, and motor rehabilitation. Additionally, G.Tec's EEG systems are fully compatible with real-time signal processing and analysis platforms, including MATLAB/Simulink, OpenViBE, and BCI2000. This interoperability facilitates the seamless integration of custom algorithms, real-time feedback loops, and BCI applications, enabling both offline and online analysis for experimental and clinical neuroscience research.

EEG data signal processing pipeline includes Fast Fourier Transform (FFT), sinusoidal decomposition, time-frequency analysis, and time-series to extract meaningful spectral features that will be divided into five canonical frequency bands, each representing distinct neurophysiological and cognitive states: Delta (0.5–3 Hz), Theta (4–7 Hz), Alpha (8–13 Hz), Beta (13–30 Hz) and Gamma (>30 Hz). All EEG recordings undergo rigorous quality control, including the rejection of segments with excessive physiological or environmental artifacts and the exclusion of sessions exhibiting poor electrode impedance or contact. This methodological rigor ensures the acquisition of high-fidelity EEG signals, suitable for accurately investigating the neurophysiological correlates of cognitive states or pain perception [44].

#### **4.2 EEG Frequency Bands in Acute and Chronic Pain**

Studies have identified distinct correlations between EEG frequency bands and both acute and chronic pain perception. Delta oscillations, typically associated with the brain's default mode network and most prominent during self-directed thought or introspection in healthy individuals, appear to be altered in patients experiencing pain, particularly in chronic conditions [45]. Increased delta power at rest has been observed in individuals with chronic pain, potentially reflecting the brain's ongoing processing of pain signals [46]. Additionally, the delta band has been proposed to contribute to pain distraction mechanisms, possibly by reducing attention to painful stimuli [47]. In patients with knee osteoarthritis, elevated delta activity has been associated with enhanced intracortical inhibition, suggesting a compensatory mechanism to modulate pain perception [32]. Supporting this view, research on individuals with brain injuries has linked low-frequency oscillations to top-down compensatory processes and improved clinical outcomes [48]. Delta power

also increases during acute pain, particularly in the frontal regions, implying its role in the cognitive and emotional dimensions of pain processing. An increase in frontal delta activity is one of the most consistently reported EEG changes during painful stimulation [49], further reinforcing the idea that heightened delta oscillations may act as a compensatory mechanism in pain modulation.

Theta band activity typically increases in response to mechanical and thermal pain stimuli, reflecting its involvement in pain processing. Conversely, alpha band power generally decreases following noxious stimuli such as cold pressor tests and laser stimulations [50]. Beta and gamma band powers tend to increase in response to heat stimuli, with gamma activity also rising after exposure to cold pressor challenges [51]. Beta oscillations, in particular, have been associated with pain intensity across various chronic pain conditions. For example, in patients with knee osteoarthritis, enhanced beta activity in the frontal brain regions correlates with higher pain intensity [32]. Similarly, individuals with fibromyalgia exhibit increased connectivity and activity in the beta-3 frequency band, which has been implicated in sensory, affective, and attentional components of pain processing [52]. In cases of chronic neuropathic pain (CNP), pain reduction has been positively associated with increased alpha power, whereas pain exacerbation is linked to elevated theta, delta, and beta activity. Furthermore, relief from chronic pain has been associated with significant increases in delta, theta, and alpha power in the frontal regions of the brain [53]. However, it is essential to note that these EEG-pain relationships may not be universally applicable across all types of chronic pain, highlighting the complex and condition-specific nature of neurophysiological pain signatures.

These spectral changes suggest that EEG is capable of objectively reflecting pain processing through frequency-specific neural dynamics. The content of these EEG signals, specifically their frequency and amplitude, fluctuates depending on various factors, including alertness, mental state, age, medication, and physical health [49]. Therefore, EEG analysis provides reliable and relevant information regarding brain function during rest, sensory stimulation, and cognitive engagement [54].

A consistent EEG finding in chronic pain is an increase in theta band power, which the thalamocortical dysrhythmia model explains. This model posits that disrupted rhythmic interactions between the thalamus and cortex are a mechanism for persistent pain [55-57]. A review by Zebhauser et al. [58] analyzing 76 studies reported not only elevated theta power but also increased beta and gamma activities, enhanced theta connectivity, and a general slowing of peak alpha frequency (PAF). Chronic pain patients consistently exhibit lower PAF compared to healthy individuals, and this reduction is correlated with pain duration, suggesting its utility as a biomarker for pain chronification. Moreover, a hallmark finding in these individuals is a shift in the dominant peak of the power spectrum toward lower frequencies, indicating altered cortical dynamics compared to healthy controls [46].

These findings were further supported by Zis et al. [49], who reported abnormal gamma oscillations linked to chronic pain, likely reflecting heightened high-frequency activity associated with enhanced sensory processing and ongoing pain sensations. Moreover, graph theoretical analyses have revealed increased frontal connectivity patterns and disrupted network organization in chronic pain patients, with changes in transitivity, betweenness centrality, intramodular degree, and rich-club coefficients; however, global properties such as small-worldness and modularity appear intact [59].

## **5. Other EEG Biomarkers Regarding Chronic Pain Oscillations**

Pain is believed to alter cortical functioning, which significantly modifies information processing at the brainstem and thalamic level, producing changes in the rhythmic bursts of brainwaves that are expressed in EEG spectral power [60, 61]. This alteration plays a key role in nociceptive processing and the modulation of sensory information, reflecting disrupted neuronal communication and pain processing. Several physiological alterations occur in chronicity of pain.

### **5.1 Brainstem-Level Changes**

The brainstem is a relay centre for transmitting nociceptive signals from the spinal cord to higher brain regions. Chronic pain induces abnormal patterns, particularly in low-frequency bands such as delta and theta, associated with amplifying pain signals. In delta oscillation, increased power in the brainstem was observed during chronic pain states, reflecting a maladaptive cortical response that signifies heightened vigilance and ongoing nociceptive processing. These changes may be related to the continuous relay of pain signals to the thalamus and cortical regions [62]. While for theta oscillations, enhanced theta activity was found in the brainstem, indicating heightened cognitive and emotional engagement with pain, as this frequency band is involved in the integration of sensory and affective components of pain [63].

### **5.2 Thalamic-Level Changes**

The thalamus is the relay centre for sensory information, including nociception. Chronic pain is associated with the dysregulation of thalamocortical rhythms, resulting in altered communication between the thalamus and the cortex. Thalamocortical Dysrhythmia (TCD) may occur, disrupting the balance between excitatory and inhibitory signals in the thalamus, resulting in abnormal low-frequency oscillations such as increased delta and theta power. TCD is often accompanied by decreased alpha and beta oscillations, reflecting a state of cortical overactivation and impaired sensory gating [64].

### **5.3 Gamma Oscillations**

Gamma oscillations have recently been identified as a potentially essential neural response to pain. Several human studies have shown a strong correlation between gamma oscillations and pain perception [65, 66], while more recent preclinical research in rodents supports the consistency of this relationship across species [67-69]. Notably, gamma oscillations appear to be pain-specific, as they are not elicited by other types of stimuli, such as visual or auditory inputs. Moreover, gamma oscillations induced by laser stimulation at different energy levels to minimally conscious patients were then measured, and pain response and EEG gamma power resulted in higher pain scores and increased gamma activity, suggesting the patients were consciously processing pain. Additionally, reduced gamma oscillations in the thalamus may occur in chronic pain, as they have been linked to impaired integration of sensory information and altered perception of pain intensity. This reduction reflects the thalamus's inability to effectively synchronize with cortical regions involved in pain processing [70, 71].

The persistent low-frequency oscillations of delta and theta in the brainstem and thalamus may amplify nociceptive signals, thereby increasing the perception of pain. Concurrently, the disruption

of high-frequency oscillations of beta and gamma in the thalamus impairs the brain's ability to filter and integrate sensory input. This disruption leads to a maladaptive pain state characterized by heightened pain sensitivity (hyperalgesia) and pain from non-painful stimuli (allodynia) [72].

#### **5.4 Event-Related Desynchronization/Synchronization (ERD/ERS)**

Event-Related Desynchronization (ERD) and Event-Related Synchronization (ERS) offer a dynamic perspective on how brain wave patterns evolve in response to painful stimuli. It shows the underlying neural network or neural circuitry works in a desynchronized or synchronized manner, reflecting an attenuation or increase of the amplitude or strength of the continuous EEG waveforms [60]. ERD reflects an increased excitation of cortical oscillations and has been linked to various pathophysiological processes in the basal ganglia, suggesting impaired dopaminergic modulation. In EEG-based studies on pain processing, enhanced ERD has been observed during attention to painful stimuli, indicating the involvement of thalamocortical circuits in the attentional modulation of pain [73]. Conversely, ERS characterised by an increase in power, represents cortical deactivation which may serve to mitigate pain perception. Notably, higher pain thresholds have been positively correlated with alpha ERS [74], suggesting a potential protective role in pain processing. Analyzing ERD/ERS patterns reveals how different brain regions contribute to the perception and modulation of pain. For example, alpha ERD in the sensory-motor cortex may correspond to attentional shifts to the pain stimulus, while beta ERS could indicate inhibitory feedback mechanisms [75]. These oscillatory changes provide a nuanced understanding of the brain's dynamic response to nociceptive stimuli.

#### **5.5 Peak Alpha Frequency (PAF)**

Peak Alpha Frequency (PAF) refers to the frequency within the alpha band (8–13 Hz) that exhibits the highest spectral power [76]. As pain is a complex and individualized experience, PAF has emerged as a potential neurophysiological biomarker for pain sensitivity and processing [77]. Higher PAF is typically associated with increased cortical excitability and cognitive performance, including superior working memory and finer temporal visual resolution [78]. PAF generally increases throughout development and reflects both state- and trait-related brain function.

In pain research, distinct PAF patterns have been observed between acute and chronic pain conditions. In individuals with chronic pain such as central, visceral, or neuropathic pain, PAF is often slowed relative to healthy controls, potentially due to thalamocortical dysrhythmia or neuroplastic adaptations from persistent nociceptive input [79]. Conversely, acute pain has been associated with transient increases in PAF, and higher baseline PAF has been linked to greater sensitivity to pain in healthy individuals, suggesting that PAF may signal both current pain states and predisposition to chronic pain development [77].

A recent study by Martino et al. [80] further supports the role of PAF in pain processing, showing that central PAF slowed progressively during repeated muscle contractions that induced pain across several days. This finding indicates that sustained pain can modulate alpha dynamics, possibly reflecting adaptive cortical integration of ongoing nociceptive input. Interestingly, individuals with greater pain sensitivity exhibited faster central PAF during pain exposure, which may reflect individual differences in cognitive or emotional responses to pain. These results highlight the

relevance of PAF as a dynamic biomarker of prolonged pain sensitivity and individual variability in pain experience.

## **6. Toward Objective and Real-Time Pain Monitoring**

The development of EEG-based pain biomarkers offers a promising pathway for objective pain assessment, particularly for non-verbal populations such as infants or unconscious patients. The capacity of EEG to capture real-time brain activity enables its integration into closed-loop neuromodulation systems for responsive pain management. Compared to other neuroimaging modalities, such as PET, NIRS, and MRI, EEG's superior temporal resolution, non-invasiveness, and cost-effectiveness [81] make it an ideal candidate for point-of-care applications in clinical pain monitoring and management.

Electroencephalography is the most cost-effective measure that can yield millisecond-level information about the timing of pain-related signals and pain-associated brain oscillations. Biomarkers can reveal pain-causing mechanisms of disease in brain circuits. Understanding this concept of pain promises insights into how flexible routing of information flow coordinates diverse processes that merge into the experience of pain. Such insight paves the way for understanding and treating this disorder. Although few studies reported, the pain matrix was centred in the thalamus, whereby the source of information brought through the lateral spinothalamic tract in the spinal cord [82], and quantitative EEG demonstrated specific increases in neuronal activity in the thalamus, somatosensory cortex, anterior and posterior insula, medial and lateral prefrontal cortex, and cingulate. Advances in technology now enable the analysis of brain oscillations, providing insights into the neurophysiological mechanisms underlying pain. This progress can potentially make pain assessment more objective, leading to more accurate and personalized treatment. In this review, we examine the arguments supporting the use of EEG as a reliable tool for objective pain measurement.

In recent years, advancements in neuroscience and neuroimaging have increasingly focused on leveraging brain–computer interface (BCI) technology for objective pain detection [83-85]. These studies highlight the potential of EEG-based BCI systems as reliable tools for measuring and assessing pain by developing models that detect and classify pain severity using EEG signals. Machine learning (ML), a fundamental domain within artificial intelligence (AI), along with deep learning (DL), offers powerful approaches for analyzing neural data, enabling systems to learn from experience without explicit programming. Notably, the integration of Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs) has shown promise in enhancing the robustness of pain feature detection [86].

EEG, despite its advantages such as portability, cost-effectiveness, and the ability to generate large volumes of data, has certain limitations that must be taken into consideration. EEG has limitations due to its low spatial resolution, making it difficult to precisely localize the source of neural activity, such as intense brain structures. The brain's electrical signals must pass through several layers before reaching the EEG electrodes, which are attached to the scalp, resulting in signal distortion due to the biological tissues. The meninges, cerebrospinal fluid, skull, and scalp attenuate the electrical signals that pass through them, reducing the accuracy of source localization and influencing interpretation. This transmission results in signal attenuation and distortion, making it challenging to precisely localize the source of neural activity, particularly in deep brain structures.

As a result, EEG is highly sensitive to cortical activity but significantly less effective in detecting signals from subcortical regions such as the thalamus, hippocampus, and brainstem. Moreover, EEG captures the summated postsynaptic potentials of large populations of neurons rather than individual action potentials, making it ideal for analyzing oscillatory brain activity but less suitable for detecting rapid, single-neuron events. These limitations can affect the accuracy of source localization and the interpretation of neural dynamics [87].

## **7. Conclusion**

Electroencephalography (EEG) offers a powerful and non-invasive approach for objectively assessing pain by capturing real-time neural activity. Unlike hemodynamic-based imaging techniques, such as fMRI, which infer brain activity through changes in blood flow, EEG directly records electrical signals from the brain, enabling high temporal resolution analysis. When post-processed into spectral power dynamics, event-related desynchronization (ERS) and event-related synchronization (ERS), peak alpha frequency (PAF), and other neural markers, EEG provides critical insights into the brain's response to pain. Combined with advanced analytical techniques such as machine learning and deep learning, EEG enables the identification of complex neural signatures that differentiate between pain intensities and distinguish acute from chronic pain states. The integration of EEG biomarkers with computational models holds significant promise for developing reliable, objective, and automated pain assessment tools, ultimately improving clinical pain management and enhancing patient outcomes.

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## **Author Contributions**

Dr Samhani Ismail and Muhammad Hakimi Mohd Nashron drafted the manuscript. Dr Mohd Hanifah and Associate Professor Dr Abdul Nawfar Sadagatullah were involved in planning and supervised the project. Dr Samhani Ismail outlined the graphical abstract, get consensus from all the authors.

## **Competing Interests**

The author affirms that this research was carried out without any commercial or financial interests that could be perceived as a potential conflict of interest.

## **AI-Assisted Technologies Statement**

The authors declare no generative AI tool was used during the preparation of this manuscript. The authors utilized the ChatGPT to only refine the language. We take full responsibility for the final content of this publication.

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