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Pain biomarkers based on electroencephalogram: Current status and prospect

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Highlights

- During the perioperative period, electroencephalography (EEG) has significant advantages as a tool for pain as sessment. The applications of indicators such as the pain threshold index (PTI) and γ wave activity in preopera tive, intraoperative, and postoperative pain assessment have been validated, contributing to the optimization of perioperative analgesic strategies.
- CEEG showed that pain intensity was negatively correlated with α wave activity and positively correlated with γ wave activity.
- Analysis of the characteristics of EEG in pain state is helpful for the diagnosis and treatment of pain, and to prevent the transformation of chronic pain.
- Comparing different EEG pain biomarkers can enhance the understanding of brain activity in pain state and im prove the accuracy of data.

Abstract

Pain is a subjective and complex symptom, making its prediction, management, and treatment a significant challenge in clinical research. To address these challenges, the search for reliable and objective pain biomarkers has become a focal point in pain studies. Electroencephalography (EEG), a non-invasive clinical tool, has emerged as the most widely used method for assessing brain regions associated with pain due to its temporal resolution, accuracy, and comprehensive nature. Multichannel EEG is now a primary technique in the study of pain biomarkers. This review discusses the current status and future prospects of EEG biomarkers in pain research, synthesizing evidence on the potential of EEG recordings as reliable biomarkers for pain perception. This will contribute to establishing a more solid foundation for the prediction, diagnosis, and intervention of pain in future research and management.

Keywords: Pain, electroencephalography, biomarker

Introduction

Pain, an unpleasant sensory and emotional experience, varies greatly among individuals and is a common complication following surgical procedures [1]. Studies have revealed that over 60% of surgical patients experience moderate to severe acute postoperative pain [2]. Recently, the quest for objective measures to enhance pain assessment and treatment has garnered increasing attention [2]. Despite this, the identification of uniform and reliable pain biomarkers remains elusive, with different biomarkers serving various functions such as diagnosis, monitoring, and treatment. The recognition of changes in brain structure and function has

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led to a growing interest in developing brain-based pain biomarkers using neuroimaging and electrophysiological methods. Compared to other brain imaging techniques like functional magnetic resonance imaging (fMRI), electroencephalography (EEG) offers advantages such as portability, convenience, and high temporal resolution, making it a widely used tool in assessing brain function [3, 4].

EEG biomarkers of pain typically focus on specific brain regions associated with nociception, such as the somatosensory cortex and the anterior cingulate cortex. Activity patterns in these regions can be distinguished from those related to non-nociceptive sensations, such as touch or thermal perception [5]. For instance, pain is often linked to higher frequency EEG activity, like gamma band oscillations, whereas other sensations may elicit activity at different frequencies. Although emotional states can also influence EEG signals, these effects are generally reflected in brain regions related to emotional processing, such as the prefrontal cortex and amygdala, rather than in core pain processing regions [6]. Pain-related EEG features, such as decreased alpha waves and increased gamma waves, show significant differences compared to EEG changes induced by emotional states, thereby enhancing the specificity of EEG in distinguishing between pain and emotional states.

This article aims to illustrate the reliability of EEG signals as predictive biomarkers for pain by synthesizing evidence from relevant literature and exploring the potential of quantifying pain through EEG measurements. This will significantly enhance clinical pain management and contribute to the development of new therapeutic approaches.

EEG

EEG signals, generated by neuronal discharges from the pyramidal cells of the cerebral cortex, reflect the physiological processes of neurons in the brain and contain rich information about brain activities [7-9]. This technology has achieved significant advancements in clinical practice, including the assessment of cognitive function, diagnosis of epilepsy, and monitoring of anesthesia depth. The EEG acquisition system, based on a high-precision analog-to-digital converter, captures minute signal changes emitted by electrodes on the scalp surface. The acquired pain signals are then decoded through time-frequency domain analysis and other EEG techniques, revealing cortical loops involved in pain processing and analysis. Quantifying the correlation between the somatosensory cortex and pain from different topographic maps and waveform features deepens our understanding of pain-related EEG signals, making it a valuable tool for pain prediction, diagnosis, and treatment in clinical settings [4, 8, 10]. However, in practical applications, EEG data collection is inevitably subject to noise and artifacts due to external environmental interference. Some artifacts can be effectively removed during data preprocessing, and preventive measures can also be taken to avoid artifacts caused by unnecessary movements.

In recent years, studies have focused on quantifying pain through algorithmic analysis of EEG data characteristics, resulting in various derivative indices. The clinical application of these indices has been effectively demonstrated, with EEG also being used to study changes in brain oscillatory activity and functional connectivity across different frequencies. Pain-related EEG rhythms primarily involve changes induced by oscillations in the gamma-band (30-100 Hz), theta-band (4-7 Hz), and alpha-band (8-13 Hz) [11, 12]. Among these, gamma-band oscillations are considered one of the most promising biomarkers for pain perception, while the peak alpha frequency (PAF) is a significant biomarker for predicting pain sensitivity [13, 14]. Finally, literature suggests that microstate analysis of EEG is capable of quantifying resting-state EEG recordings into sequences of a finite number of microstates to explain changes in brain function in patients with chronic pain [15].

EEG biomarkers of pain states

Electroencephalogram derivative index

The EEG-derived indices are generated from raw EEG features and converted into dimensionless values through algorithmic analysis, reflecting changes in brain activity. Clinically, one of the most commonly used EEG-derived indices is the Bispectral Index, which is employed to assess sedation levels and monitor the depth of anesthesia. Recent studies have demonstrated that EEG-derived indices can also serve as biomarkers for pain, helping to predict and quantify pain responses [16]. Commonly used pain indices include the Pain Threshold Index, the Surgical Pleth Index, and the Wavelet Index. These indices aid physicians in monitoring patients' responses to nociceptive stimuli during general anesthesia and guide postoperative pain management, particularly in predicting postoperative pain in both adults and children [17]. Among them, Pain Threshold Index, through the use of wavelet algorithms, achieves temporal and spatial resolution coor-

dination of EEG signals and extracts objective quantitative features related to pain. It provides a reliable basis for predicting postoperative pain and hemodynamic responses. In recent years, studies have confirmed the significant advantages of Pain Threshold Index in predicting acute postoperative pain in both pediatric and adult populations and its effectiveness in guiding opioid dosage [18-20].

However, some studies have indicated that certain EEG indices, such as quantium nociception index, are not effective in predicting acute postoperative pain, possibly because they assess the depth of anesthesia rather than pain itself [21]. Furthermore, these EEG-derived indices are mostly measured under general anesthesia and are not applicable in awake states, as their values significantly increase during arousal and are prone to interference from medications and medical conditions. The accuracy of these indices may be affected by the influence of anesthetics and analgesics, limiting their utility in preoperative and postoperative pain assessments. In contrast, raw EEG neural oscillations, used as pain biomarkers, can compensate for these limitations, providing more objective assessments of pain, better predictive value, and aiding in the development of new pain management approaches.

α waves

To date, oscillatory activity in EEG frequencies has been repeatedly shown to play a significant role in experiments involving pain stimulation in healthy subjects. Recent studies have indicated that neuronal responses related to pain are primarily concentrated in α-frequency, γ-induced responses, and θ-evoked responses, further supporting the feasibility of EEG as a tool for predicting pain and analgesic responses [11]. In the resting state, changes in α-wave activity are the most commonly observed. When the body is subjected to pain stimuli, α-frequency in the frontal and parieto-occipital regions is considered an important biomarker. Clinical data have shown that in healthy individuals, α-frequency increases in response to acute pain stimulation, while in chronic pain patients, α-frequency tends to decrease [11, 22].

In the past decade, the mainstream method for pain-related EEG research has been using experimental pain paradigms (e.g., laser or thermal pain stimulation) to assess evoked potentials in response to brief nociceptive stimuli [23]. Time-frequency analysis has further expanded the scope of evoked potential studies, with most experiments converting the time-domain data of pain EEG signals into the frequency domain, yielding the PAF as a key measurement. Furman et al. used a "capsaicin-heat pain" model to simulate the transition from a pain-free state to persistent pain in healthy subjects, demonstrating that PAF is negatively correlated with postoperative pain intensity in both pain-free and persistent pain states [22]. Subsequently, De Martino et al. investigated muscle pain through intramuscular injection of nerve growth factor, finding that PAF significantly slowed during muscle contraction and in the state of prolonged muscle pain [24]. These findings are consistent with previous experimental pain studies, which showed that during sustained skin pain, the amplitude or peak frequency of α-oscillations decreased, suggesting that PAF slowing could serve as a potential biomarker for pain sensitivity and provide insights into the transition from acute to chronic pain. Although PAF has been demonstrated as a biomarker for pain, its reliability remains a subject of debate. Previous studies have shown that PAF can remain stable over time, but fluctuations in α-wave energy induced by pain may affect its predictive accuracy [25, 26]. A recent study explored the effects of frequency window selection, EEG recording time, and peak identification methods on PAF stability, showing minimal impact from these factors and confirming the reliability of PAF in predicting pain sensitivity [26]. However, most studies have been conducted on healthy individuals in response to experimental pain, and the relationship between α-frequency and clinical pain in patients still requires further investigation.

In recent years, although EEG technology has become increasingly sophisticated in pain research, evidence linking EEG with postoperative pain remains limited. A study conducted in lung cancer patients with no or mild pain found that PAF, measured in the preoperative awake state, demonstrated high sensitivity and specificity in predicting postoperative acute pain [14]. PAF could be used as a clinical tool for stratifying pain-sensitive patients and predicting postoperative acute pain, with preoperative PAF negatively correlated with postoperative pain intensity. This finding contrasts with the increase in α-frequency observed in response to acute pain stimulation in healthy individuals, possibly due to the fact that pain induced by external nociceptive stimuli does not fully represent acute pain but rather reflects a transition from acute to chronic pain. Additionally, a study by de Vries et al. in patients with chronic pancreatitis showed that the longer the duration of pain, the greater the reduction in PAF, as assessed through comparisons of PAF and power

amplitude in specific regions of interest during the awake state [27]. Thus, PAF may also serve as a marker of the progression from acute to chronic pain.

In summary, whether in experimental or clinical pain research, these findings provide important insights into the prediction of acute pain and the diagnosis and treatment of patients with chronic pain. The reduction of PAF is associated with persistent abdominal pain caused by chronic pancreatitis, neuropathic pain resulting from spinal cord injury, and acute pain following postoperative trauma. PAF shows significant potential as a reliable clinical biomarker for predicting pain intensity in preoperative pain-free patients or those experiencing mild pain.

γ waves

In the field of neuroscience, gamma oscillations are considered an important characteristic of cortical activity, not only closely related to cognitive functions such as learning, attention, and memory, but also significantly associated with subjective pain ratings, stimulus intensity, and pain perception [12]. Evidence suggests that gamma-band oscillations measured through scalp EEG are one of the most selective biomarkers for reflecting both stimulus-evoked and spontaneous pain perception intensity [13].

Literature indicates that gamma oscillations in the primary somatosensory cortex induced by pain are significantly correlated with subjective pain experiences [11, 12, 28]. Since the amplitude of gamma band oscillation (GBO) is directly related to subjective pain intensity, studies suggest that these oscillations reflect cortical activity directly linked to pain perception. In pain-free patients or those with mild pain, gamma oscillations recorded in the awake state before surgery can encode individual pain sensitivity and predict postoperative changes in subjective pain intensity [29]. Most studies on gamma activity during pain stimulation have shown a significant increase in energy [30]. A preoperative measurement of gamma frequency to predict acute postoperative pain found that patients in the moderate-to-severe pain group had significantly higher gamma frequencies than those in the low-pain group, indicating that preoperative EEG data could effectively identify patients at high risk of postoperative pain [31]. However, due to the high frequency of gamma waves, they are susceptible to external environmental interference during signal acquisition, and when using high-pass filters for data processing, gamma waves may be mistakenly removed as noise artifacts. Therefore, although gamma oscillations have the potential to be a biomarker for pain prediction, many challenges still exist in clinical trials. The effective elimination of such interference remains a critical issue for future research to address.

Other frequency bands of EEG activity

Resting-state EEG studies have shown that changes in α-frequency and θ-band power, as well as increases in β-band power during pain, occur in the frontal, parietal, temporal, and occipital cortices [27]. In normal brains, θ waves are associated with functions such as intuition, creativity, and imagination; δ waves increase significantly during deep sleep or coma; low-frequency β waves are related to focused attention, while high-frequency β waves are linked to alertness and agitation [32]. As research progresses, the relationship between these brainwave activities and pain is becoming clearer, and they all have the potential to serve as clinically useful biomarkers for pain. Clinical data suggest that the relationship between θ wave activity and pain is somewhat contradictory. Some studies have found that θ wave power increases in response to brief pain stimulation, chronic pain, or neuropathic pain [11, 33-35]; other studies, however, have indicated that pain stimulation leads to reduced θ activity [36, 37]. Additionally, research has shown an increase in θ power in cold pain stimulation models [38, 39]. Despite these discrepancies, most studies agree that pain stimulation elicits increased δ and β wave activity, although some literature has presented differing views [38, 39]. While these relationships between various EEG frequency bands and pain have been observed, whether they can serve as convincing and clinically useful biomarkers for pain remains to be further validated. Given the complexity of pain, along with the differences in its types, intensity, duration, and location, EEG changes induced by pain vary greatly. Future studies will need to conduct in-depth analyses of the changes in different EEG frequency bands and explore their relationships with patients' clinical symptoms.

An increasing body of evidence suggests that oscillatory patterns in different brain regions, as well as their synchronization, play a critical role in both acute and chronic pain [40]. The study and development of biomarkers are considered key steps in the prediction and treatment of pain. To further develop the potential of EEG signals as biomarkers for pain, distinguish between biomarker types, and assess their specificity, this review also introduces an additional EEG analysis method, microstate analysis. As

Table 1. The relationship between EEG frequency and pain

EEG Rhythm	Frequency Range	Relation to pain
Delta	0.5-4 Hz	Increased in deep sleep or unconscious states; not directly related to pian but can be elevated in chronic pain conditions [32, 38].
Theta	4-8 Hz	Often increased during pain anticipation and chronic pain; related to emotional processing and attention [33-35].
Alpha	8-13 Hz	Decreased in response to acute pain; associated with relaxation and inhibitory processes [11, 22].
Beta	13-30 Hz	Increased during states of alertness and cognitive processing; can be elevated in anticipation of pain [32].
Gamma	30-100 Hz	Increased during acute pain; associated with the perception of pain and processing of nociceptive information [28-30].

Note: EEG, Electroencephalography.

shown in **Table 1**.

Microstate analysis of pain monitored by EEG

Microstates are brief, patterned brain topographies observed in resting-state EEG recordings, representing functional brain networks. Microstates remain stable before rapidly transitioning to another functional network and can reflect pain perception and the temporal dynamics of the brain [15, 41]. As such, EEG microstates are considered valuable tools for assessing brain function, offering important insights into pain perception by capturing momentary changes in brain activity.

A study utilizing closed-eye resting-state EEG microstate analysis to evaluate chronic pain showed that, compared to healthy individuals, microstate D was reduced in chronic pain patients, while no significant microstate changes were observed in patients with chronic widespread pain [39]. Another study found that, in patients with chronic widespread pain, the occurrence and time coverage of microstate C were lower in resting-state EEG recordings with open eyes [42]. This discrepancy may stem from differences in methodology and sample size or reflect that the brain activity changes revealed by microstate analysis are specific to certain types of pain. These findings support the use of EEG microstates as biomarkers of chronic pain and in analyzing brain function changes and potential pathological dynamics. However, further research is needed to better elucidate the specificity of microstate changes in different chronic pain populations. Additionally, Li et al. performed clustering and time-feature analysis on resting-state EEG microstates in breast cancer patients during the preoperative awake state, finding that patients prone to postoperative pain exhibited higher occurrence and coverage of microstate C, which was positively correlated with scores of the numeric rating scale [43].

In summary, these studies support the novel idea that EEG microstates can serve as windows into specific differences in brain networks related to pain and may be used as brain biomarkers of pain. Although current research suggests a link between EEG microstates and pain sensitivity, the nature of this relationship is inherently complex, and many brain mechanisms associated with pain sensitivity remain to be discovered.

Discussion

This review summarizes the evidence supporting EEG as a biomarker for pain and highlights the differences between potential biomarker types. Although the use of EEG-derived indices has some limitations, and the correlation between certain oscillatory activities and pain remains controversial, numerous studies have validated that pain intensity is negatively correlated with alpha-band activity and positively correlated with gamma-band activity. Additionally, EEG microstate analysis has opened new perspectives in the study of EEG pain biomarkers, demonstrating that EEG technology can provide objective and reliable biomarkers to complement patients' subjective reports of pain intensity.

In clinical practice, the use of EEG requires placing multiple electrodes on the scalp or wearing an electrode cap, and using conductive gel or saline solution to maintain good conductivity. Compared to devices such as magnetoencephalography or fMRI, EEG has a relatively lower signal-to-noise ratio, necessitating complex data analysis and large sample sizes to extract useful information from EEG data. Therefore, some studies have combined EEG with other techniques to improve the accuracy of pain detection [44, 45]. EEG has high temporal reso-

lution, while fMRI offers high spatial resolution. Combining the two can more accurately predict the subjective experience of pain and better identify brain regions associated with pain [44]. Near-Infrared Spectroscopy is a technique that evaluates neural activity by measuring oxygen levels in the brain. Studies have shown that combining EEG and Near-Infrared Spectroscopy can enhance the detection accuracy of pain responses, particularly in clinical settings such as during surgery or monitoring of chronic pain patients [45].

The advancement of EEG has allowed researchers to investigate functional connectivity in different brain regions during pain states, contributing to the construction of EEG-based pain prediction models. While clinical monitoring of pain biomarkers includes various techniques such as Bispectral Index, Surgical Pleth Index, EEG, Magnetoencephalography, and fMRI, integrating EEG-based pain monitoring into clinical practice remains a crucial step forward. Therefore, anesthesiologists should enhance their understanding of EEG-based pain monitoring techniques and actively apply them in clinical settings. Currently, several tools and software packages for EEG data acquisition and analysis are available, such as Brain Vision Recorder, Matrix Laboratory (MATLAB), and the EEGLAB (Electrical and Elastic Glass Brain Analysis Lab) toolbox. Anesthesiologists need to become proficient in using these tools, including how to acquire EEG signals and perform data analysis and processing. Developing new therapeutic techniques based on EEG technology, which target specific symptoms, reduce side effects, and improve patient compliance, is a key direction for future pain research. Identifying the EEG rhythms that should be modulated to achieve optimal analgesia is crucial to the success of these therapeutic strategies.

Conclusion

This review summarizes the potential of EEG as an objective biomarker for pain assessment and management. By analyzing EEG features such as α-wave suppression, γ-wave enhancement, and EEG-derived indices, it provides valuable insights into pain perception, sensitivity, and the transition from acute to chronic pain. Particularly during the perioperative period, EEG demonstrates significant value in predicting postoperative pain, optimizing analgesic strategies, and guiding personalized pain management. Despite challenges such as signal noise, environmental interference, and the effects of anesthetics, the integration of advanced techniques like microstate analysis and combination with fMRI and Near-Infrared Spectroscopy offers improved precision in pain assessment. Future research should focus on addressing these limitations to promote the widespread clinical application of EEG biomarkers, thereby enhancing patient outcomes.

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