Review article

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Advances, challenges, and prospects of electroencephalography-based biomarkers for psychiatric disorders: a narrative review

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Owing to a lack of appropriate biomarkers for accurate diagnosis and treatment, psychiatric disorders cause significant distress and functional impairment, leading to social and economic losses. Biomarkers are essential for diagnosing, predicting, treating, and monitoring various diseases. However, their absence in psychiatry is linked to the complex structure of the brain and the lack of direct monitoring modalities. This review examines the potential of electroencephalography (EEG) as a neurophysiological tool for identifying psychiatric biomarkers. EEG noninvasively measures brain electrophysiological activity and is used to diagnose neurological disorders, such as depression, bipolar disorder (BD), and schizophrenia, and identify psychiatric biomarkers. Despite extensive research, EEG-based biomarkers have not been clinically utilized owing to measurement and analysis constraints. EEG studies have revealed spectral and complexity measures for depression, brainwave abnormalities in BD, and power spectral abnormalities in schizophrenia. However, no EEG-based biomarkers are currently used clinically for the treatment of psychiatric disorders. The advantages of EEG include real-time data acquisition, noninvasiveness, cost-effectiveness, and high temporal resolution. Challenges such as low spatial resolution, susceptibility to interference, and complexity of data interpretation limit its clinical application. Integrating EEG with other neuroimaging techniques, advanced signal processing, and standardized protocols is essential to overcome these limitations. Artificial intelligence may enhance EEG analysis and biomarker discovery, potentially transforming psychiatric care by providing early diagnosis, personalized treatment, and improved disease progression monitoring.

Keywords: Artificial intelligence; Biomarkers; Electroencephalography; Mental disorders

Introduction

Psychiatric disorders cause significant distress and functional impairment, resulting in substantial social and economic losses totaling 5 trillion US dollars [1]. The individual suffering and socioeconomic burden are, to a considerable extent, attributed to the lack of appropriate biomarkers for accurate diagnosis and treatment. The absence of suitable biomarkers leads to delayed initiation of treat-

ment or interruption during treatment [2]. A biomarker is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention" [3]. Biomarkers play crucial roles in the diagnosis, prediction, treatment, and monitoring of diseases. Consequently, a wide range of biomarkers has been utilized in various fields, and active research is dedicated to the development of novel biomarkers [4]. The lack of useful psychiatric biomarkers is closely

linked to the complex structures and functions of the brain. Additionally, a significant contributing factor is the lack of appropriate modalities for direct monitoring of brain function [5]. Therefore, various neuroimaging and neurophysiological modalities are used to indirectly assess brain function to identify biomarkers for psychiatric disorders [6].

Electroencephalography (EEG) is a widely used neurophysiological modality for studying psychiatric biomarkers [7]. EEG measures the electrophysiological functions of the brain and primarily reflects the synaptic activity of pyramidal cells [8]. By attaching electrodes to the scalp, EEG noninvasively monitors brain function, making it a valuable tool that has historically been used for diagnosing various neurological disorders, such as epilepsy and narcolepsy, and for treatments such as neurofeedback [9]. Additionally, EEG is a useful modality in research areas such as brain-computer interfaces and cognitive neuroscience [10]. Consequently, it is actively used in research aimed at identifying biomarkers that are lacking for various psychiatric disorders, such as depression, bipolar disorder (BD), and schizophrenia [11]. EEG-based biomarkers are valuable not only for the diagnosis and treatment of psychiatric disorders but also for understanding their pathophysiology. For example, in attention deficit hyperactivity disorder (ADHD), research using EEG biomarkers has improved our understanding of disorder's heterogeneity [12]. In autism spectrum disorder, studies utilizing EEG biomarkers have provided insights into the core pathologies of mirror neuron dysfunction and sensory processing problems [13].

Despite the various potentials of EEG and the considerable amount of research conducted to date, EEG-based biomarkers have not yet been used practically in the clinical psychiatric field. This limitation can be attributed to the complexities of psychiatric disorders and several constraints in current EEG measurements and analyses [14]. However, numerous efforts across various domains have recently been made to overcome the limitations of EEG [15,16]. Therefore, this study aimed to review the existing research on identifying biomarkers for psychiatric disorders using EEG, examine the limitations of these studies, and explore potential solutions to overcome these challenges.

Investigating potential electroencephalography biomarkers for major psychiatric disorders: insights into depression, bipolar disorder, and schizophrenia

1. Depression

Depression is a mental disorder that involves emotional symp-

toms, such as depressed mood, and encompasses a variety of physical and cognitive changes, including alterations in appetite, sleep patterns, and concentration [17]. Factors that contribute to the onset of depression include genetic susceptibility, stress, and developmental trauma. However, the lack of objective biomarkers often makes it difficult to receive timely and appropriate treatment [18]. Additionally, even with pharmacological treatment, 30% to 40% of patients experience residual symptoms, making it crucial to predict treatment response; however, there are currently no adequate biomarkers [19]. Therefore, ongoing efforts have been made to use biomarkers for the diagnosis and treatment of depression, and various studies have been conducted using EEG.

In the context of using EEG as a biomarker for depression, characteristics based on Fourier transform spectral analysis have been the most extensively studied. Alpha asymmetry is a representative marker of depression based on spectral analysis, reflecting hypoactivity of alpha power in the left frontal area and hyperactivity in the right frontal area [20]. However, recent studies have suggested that these characteristics are not consistently observed and remain controversial [21]. More recently, increased gamma-band power, located in higher frequency ranges, has been identified as a novel biomarker of depression, indicating changes in the balance between brain excitation and inhibition [22]. EEG during sleep shows specific changes in individuals with depression. Specifically, patients with depression exhibit increased rapid eye movement (REM) sleep and decreased REM sleep latency. Additionally, changes in slow-wave activity related to treatment response have been identified [23]. REM sleep is characterized by changes in the theta-, beta-, and gamma-band activities [24]. Considering these characteristics, various methods based on Fourier transformation have been utilized for the automatic classification of sleep stages, including REM and slow-wave sleep [25]. Although Fourier transformation primarily reflects the linear characteristics of EEG signals, complexity measures that capture the nonlinear characteristics of EEG signals have been used in various analyses of depression [26]. Studies using various complexity measures, such as entropy and Lempel–Ziv complexity, have generally indicated higher complexity in the EEG of individuals with depression [27,28]. Lempel–Ziv complexity is a metric that reflects the complexity of time-series data, whereas entropy, based on information theory, reflects the uncertainty of time-series data. In EEG, these metrics reflect fluctuations in neural activity or spontaneous stochasticity [29-31]. Studies using event-related potentials (ERPs) have been conducted. The P300 component, which reflects cognitive processing in the brain, tends to show an increased latency and decreased amplitude during depression [32]. Furthermore, the P50 component, which reflects sensory processing, shows increased amplitude in

depression, indicating impaired sensory gating in patients [7].

2. Bipolar disorder

BD is a chronic mental illness characterized by extreme mood swings between depression and mania, affecting approximately 2.4% of the global population and primarily manifesting in early adulthood [33]. The development of reliable biomarkers is essential for the accurate diagnosis and prediction of treatment outcomes in BD and for elucidating its uncertain pathophysiology [34]. EEG provides detailed insights into brain activity through the analysis of various brainwave frequencies such as alpha, delta, theta, and gamma [35]. In patients with BD, EEG studies have identified several notable abnormalities. For example, abnormalities in alpha activity, particularly in frontocentral regions, have been associated with cognitive and sensory processing deficits [36,37]. While beta, left delta, and theta activities are normalized with lithium, treatment response is most closely associated with basal delta activity. Lithium plasma concentration correlates with theta activity [38], and delta activity is linked to attention deficit and cognitive impairment [39]. Moreover, the increased beta activity and frontal alpha asymmetry during manic episodes suggest neural excitation and mood dysregulation [40]. Similar to research on depression, studies have been conducted to identify biomarkers of BD using measures of complexity. Fernández et al. [41] used Lempel–Ziv complexity to distinguish the differences in EEG complexity between depression and BD. Additionally, Bahrami et al. [42] reported that EEG complexity increased during the manic state in BD.

3. Schizophrenia

Schizophrenia is a persistent and often debilitating mental illness that affects approximately 1% of the global population [43]. Developing biomarkers for schizophrenia is essential to provide objective diagnostic and treatment measures, validate targets, predict responses, and enable personalized treatment by identifying disease mechanisms [44]. In schizophrenia research, power spectral analysis of EEG has revealed several key abnormalities. Patients typically exhibit increased power in the delta (0.5–4 Hz) and theta (4–8 Hz) frequency bands, indicating a disruption in slow-wave activity [45]. Additionally, reduced alpha power (8–13 Hz) is commonly observed, reflecting impaired cortical inhibitory mechanisms and resting-state neural activity. Although alterations in beta power (13–30 Hz) have been reported, the findings vary, with a few studies showing increased beta activity and others showing decreased beta activity.

Consequently, various EEG-based markers have been extensively studied in schizophrenia, with a particular focus on ERPs that measure electrophysiological changes [45] following stimulation. The most studied markers are P50 sensory gating, N100, mismatch negativity (MMN), and P300, each of which provides unique insights into different aspects of brain function. P50 sensory gating reflects the ability of the brain to suppress irrelevant stimuli, with deficits indicating impaired inhibitory processes that are commonly observed in schizophrenia [46]. The amplitude of the N100 waveform, which is associated with early auditory processing, is typically reduced in patients with schizophrenia, suggesting deficiencies in sensory registration [47]. MMN, elicited by deviations in the sequence of auditory stimuli, is a robust marker of predictive coding deficits and is sensitive to N-methyl-D-aspartate receptor dysfunction, highlighting its potential as an early indicator of psychosis risk [48]. Finally, the P300 component, which is indicative of attention and memory processes, shows consistent amplitude reduction and latency prolongation in schizophrenia, correlating with cognitive impairment [49]. These EEG markers enhance our understanding of the underlying neurobiology of psychosis and offer valuable tools for early diagnosis, monitoring disease progression, and tailoring individualized treatment strategies.

Electroencephalography biomarkers in psychiatry: benefits, limitations, and developmental hurdles

1. Advantages of electroencephalography-based biomarkers in neuropsychiatric applications

EEG-based biomarkers offer several advantages for neuropsychiatric applications [50]. They enable real-time data acquisition and provide immediate feedback and continuous monitoring, which are crucial for rapid diagnosis and treatment response assessment [51]. In addition, unlike other neuroimaging techniques that indirectly measure neuronal activity through blood oxygen levels, EEG directly measures the electrical activity between neurons, which is the primary cause of psychiatric disorders [52]. EEG is noninvasive and causes minimal discomfort to patients, making it ideal for repeated measurements [53]. The noninvasive nature of EEG makes it significantly safer than other invasive methods used to diagnose neuropsychiatric disorders, such as blood sampling, cerebrospinal fluid tapping, and brain tissue biopsy. Moreover, EEG is cost-effective compared to other neuroimaging techniques, facilitating broader patient access and large-scale studies [54]. With high temporal resolution, EEG captures changes in fine-grained brain activity that are essential for understanding the mechanisms of neuropsychiatric diseases [55]. EEG is applicable for diagnosing and monitoring various conditions, including epilepsy, sleep disorders, ADHD, and schizophrenia, and can predict treatment responses and disease progression [11,40]. Integrating EEG data

with machine learning algorithms allows the development of precise diagnostic models, aiding in the creation of personalized treatment plans [2,56]. Furthermore, with appropriate data processing and analysis techniques, EEG-based biomarkers can achieve high sensitivity and specificity, making them useful for early diagnosis and evaluation of treatment efficacy [11]. These advantages highlight the significant role of EEG-based biomarkers in the diagnosis and management of neuropsychiatric disorders.

2. Challenges in the clinical application of electroencephalography-based biomarkers for psychiatric disorders

Despite their numerous advantages, EEG-based biomarkers for psychiatric disorders have several limitations that restrict their broader clinical application. First, the spatial resolution of EEG is relatively low compared with that of other neuroimaging techniques such as functional magnetic resonance imaging (fMRI), making it difficult to accurately localize neural activity, particularly in deeper or smaller brain regions [57]. This limitation can impede the precise mapping of brain functions and identification of specific neural substrates underlying neuropsychiatric conditions. Second, EEG signals are highly susceptible to interference [58]. EEG signals can be distorted by the electrical resistance of the skull and scalp and are often contaminated by external electromagnetic interference and physiological noise, such as eye blinks, muscle movements, and cardiac activity. This interference can significantly affect the quality and reliability of the recorded data, making it challenging to isolate relevant neural signals from noise. Therefore, distinct changes in EEG, such as those observed with seizures, can be detected with minimal processing and near real-time monitoring. However, the cognitive and emotional characteristics of the brain, which are primarily associated with psychiatric disorders, are highly susceptible to such noise [59]. Third, the complexity and inherent noise of EEG data make their interpretation particularly challenging [60].

Analyzing EEG data requires sophisticated signal-processing techniques and expert knowledge of neurophysiology and bioinformatics, which can be significant barriers in both clinical and research settings. However, the need for advanced analytical methods limits the accessibility and practicality of EEG-based biomarkers, particularly in settings with limited technical resources and expertise. Additionally, individual physiological differences, such as variations in skull thickness, scalp conditions, and brain anatomy, can markedly influence EEG signals [61]. These interindividual differences can lead to variability in the recorded data, thus reducing the consistency and reliability of EEG-based biomarkers. Such variability poses a significant challenge in standardizing EEG mea-

surements and ensuring that biomarkers are comparable across individuals and studies. Another critical limitation is the difficulty in standardizing EEG measurements and data processing methods [62]. Considerable variability exists in the equipment used, protocols for data acquisition, and algorithms for data analysis, which can lead to discrepancies in the results across different studies [63]. For example, high-density EEG systems, which provide more detailed spatial information, may yield different results than low-density systems, complicating the comparison and replication of findings. Finally, the clinical applicability of EEG-based biomarkers is currently limited to only a few neuropsychiatric conditions. Although significant progress has been made regarding the use of EEG biomarkers for disorders such as epilepsy, schizophrenia, and sleep disorders, the validity and reliability of these biomarkers need to be established for a broader range of conditions through extensive research and clinical validation [5]. This limitation underscores the need for further studies to explore the potential of EEG biomarkers in the diagnosis and management of other neuropsychiatric and neurological disorders. These challenges highlight the need for continued technological advancements, efforts to standardize EEG methodologies, and comprehensive research to enhance the reliability, validity, and clinical applicability of EEG-based biomarkers. Addressing these limitations is crucial for integrating EEG biomarkers into personalized medicine and for improving patient outcomes in neuropsychiatric care.

3. Challenges in biomarker development due to the complexity of psychiatric disorders

Developing EEG-based biomarkers for psychiatric disorders presents significant challenges owing to both the limitations of EEG as a modality and the inherent complexity and heterogeneity of these conditions. Unlike other medical fields, where biomarkers (such as genetic markers in Huntington's disease or breast cancer gene 1/2 mutations) provide clear diagnostic value, psychiatric disorders lack such straightforward biological markers [5]. The symptoms of psychiatric disorders are often nonspecific and overlap significantly across diagnoses, making it difficult to identify unique biomarkers [64]. For instance, symptoms of psychosis can manifest in schizophrenia, BD, major depressive disorder with psychotic features, or even because of substance abuse.

The diagnostic criteria in psychiatry, such as those outlined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, are primarily based on symptomatology rather than underlying biological mechanisms, further complicating the identification of reliable biomarkers [65]. This symptom-based approach leads to diagnostic instability, whereby a patient's diagnosis may change over time as the symptoms evolve, potentially leading to

misclassification in biomarker studies. Moreover, the lack of objective laboratory tests in psychiatry means that clinical diagnoses rely heavily on subjective clinical interviews, increasing variability and reducing the reliability of diagnoses among clinicians. This issue is compounded by the high comorbidities of psychiatric conditions, in which patients often present with multiple overlapping disorders, complicating the isolation of biomarkers specific to a single diagnosis [2]. Methodological challenges, such as small sample sizes, lack of standardization of study protocols, and need for longitudinal studies to understand the temporal relationships between biomarkers and psychiatric conditions, further hinder progress [5]. Many studies have excluded individuals with severe symptoms or high comorbidities, limiting the generalizability of their findings to broader clinical populations.

Animal models, which are instrumental in biomarker research for other medical conditions, are less effective in psychiatry because of the fundamental differences in brain structure and function between humans and animals [66]. Psychiatric disorders often involve complex cognitive and emotional processes that are difficult to replicate in animal models, thereby reducing their utility for biomarker discovery. These challenges highlight the need for large-scale collaborative research efforts that integrate multiple data types and adopt a more systematic and standardized approach to biomarker research. By addressing these methodological and clinical challenges, the field of psychiatry can move closer to identifying reliable biomarkers to improve the diagnosis, treatment, and understanding of psychiatric disorders.

Overcoming challenges in electroencephalography-based biomarker development for psychiatric disorders

Ongoing research efforts are aimed at overcoming the limitations of traditional EEG characteristics and analytical methods [67]. To address the spatial resolution limitations of EEG, researchers are exploring simultaneous acquisition with other neuroimaging modalities, such as fMRI and magnetoencephalography, as well as enhancing three-dimensional reconstruction techniques for more precise localization of brain activity [68,69]. High-dimensional EEG data present significant analytical challenges. However, leveraging large-scale open data and advanced multivariate analysis methods can help eliminate irrelevant features and highlight significant patterns [70,71]. For instance, large-scale multisite EEG big data studies, such as the ENIGMA (Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia) study, are expected to address and potentially overcome some of the current limitations of EEG [72].

Techniques such as independent component and principal component analyses are used to reduce the dimensionality of EEG data, address complexity, and improve EEG usability in clinical applications [73]. Standardized protocols, such as those developed in projects such as Brain Imaging Data Structure, are critical for integrating disparate EEG datasets, thereby enhancing the reliability of EEG-based biomarkers [74]. Additionally, artificial intelligence (AI) and deep learning technologies are revolutionizing EEG analysis by overcoming traditional limitations, aiding in the discovery of new biomarkers, and integrating different features into novel biomarker concepts [75,76]. AI-based approaches can address preprocessing challenges and enhance the predictive power of EEG signals; however, they require large sample sizes and face issues related to the interpretability of complex models [77-79].

EEG is a promising modality for AI-driven psychiatric biomarker research owing to its relatively low cost and noninvasive nature [80]. By combining EEG with other neuroimaging techniques and employing advanced data analysis methods, researchers aim to develop reliable and precise biomarkers that can significantly improve personalized treatment strategies in psychiatry [81].

Conclusion

EEG-based biomarkers offer substantial potential for advancing the diagnosis and treatment of psychiatric disorders owing to their noninvasive nature, high temporal resolution, and cost-effectiveness. This review highlights various promising EEG biomarkers for depression, BD, and schizophrenia. However, the clinical application of these biomarkers faces challenges, including limited spatial resolution, susceptibility to noise, and the complexity of psychiatric conditions. To overcome these limitations, integrating EEG with other neuroimaging techniques, enhancing signal-processing methods, and standardizing measurement protocols are essential. The incorporation of AI and machine learning can further enhance the predictive power and discovery of novel biomarkers; however, this requires large well-characterized datasets. Large-scale collaborative research efforts and the development of standardized protocols are crucial for advancing this field. Ultimately, reliable EEG-based biomarkers have the potential to transform psychiatric care by enabling early diagnosis, personalized treatment, and improved monitoring of disease progression.

Article information

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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