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Machine and Deep Learning Approaches for Migraine Diagnosis and Classification: Advances and Challenges

Migren Tanı ve Sınıflandırmasında Makine Öğrenmesi ve Derin Öğrenme: İlerlemeler ve Güçlükler

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Abstract

The diagnosis and subtyping of migraine are largely dependent on clinical criteria, with the absence of objective biomarkers being a limiting factor. This structured narrative review summarises the application of machine learning (ML) and deep learning (DL) to migraine diagnosis and classification, with a particular emphasis on electrophysiology and neuroimaging. Relevant literature was identified through targeted searches in PubMed and Google Scholar utilising key terms related to migraine, ML/DL, EEG, MRI/fMRI, PET, and classification. Most ML studies employ algorithms such as support vector machines, random forests and k-nearest neighbours, using engineered features derived from electroencephalograms (EEGs) or imaging-derived measures. In contrast, deep learning (DL) architectures, predominantly convolutional neural networks, learn representations from high-dimensional data, including EEG segments or resting-state functional magnetic resonance imaging (fMRI) features. Although many studies report high classification performance, findings are frequently limited by small and homogeneous samples, limited external validation, heterogeneous preprocessing pipelines, and potential information leakage when multiple segments per participant are not handled with subject-level splits. Neuroimaging-based approaches, including PET, provide mechanistic insight but are often impractical for routine clinical use due to cost and accessibility issues. Future research should prioritise transparent reporting, subject-level validation, multi-centre datasets, and explainable multimodal models to support clinically credible translation into headache care.

Keywords: Migraine Disorders, Classification, Machine Learning, Deep Learning, Electroencephalography, Functional Magnetic Resonance Imaging

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Öz

Migrenin tanısı ve alt tiplendirilmesi büyük ölçüde klinik ölçütlere dayanmaktadır ve nesnel biyobelirteçlerin eksikliği önemli bir sınırlayıcı faktördür. Bu yapılandırılmış anlatı derlemede, makine öğrenmesi (ML) ve derin öğrenme (DL) yöntemlerinin migren tanısı ve sınıflandırmasındaki uygulamaları, özellikle elektrofizyolojik ve nörogörüntüleme temelli çalışmalar odağında özetlenmiştir. İlgili literatür, migren, ML/DL, EEG, MRI/fMRI, PET ve sınıflandırma anahtar sözcükleri kullanılarak PubMed ve Google Scholar veri tabanlarında yapılan hedefli taramalarla belirlenmiştir. ML çalışmalarının büyük çoğunluğunda destek vektör makineleri, rastgele ormanlar ve k-en yakın komşu gibi algoritmalar, EEG sinyallerinden veya görüntüleme temelli ölçütlerden türetilen özellikler kullanılarak uygulanmaktadır. Buna karşılık, çoğunlukla evrişimli sinir ağlarından oluşan DL mimarileri, EEG segmentleri veya istirahat hâli fonksiyonel manyetik rezonans görüntüleme (fMRI) verileri gibi yüksek boyutlu verilerden temsil öğrenimi yapmaktadır. Çalışmaların birçoğunda yüksek sınıflandırma performansları bildirilmekle birlikte, bulgular sıklıkla küçük ve homojen örneklemler, dış doğrulama eksikliği, heterojen önişleme süreçleri ve bir katılımcıdan elde edilen çoklu segmentlerin özne düzeyinde ayrılmaması durumunda ortaya çıkabilecek bilgi sızıntısı riski ile sınırlıdır. PET gibi nörogörüntüleme yaklaşımları mekanistik açıdan değerli bilgiler sağlamakla birlikte, maliyet ve erişilebilirlik nedeniyle rutin klinik kullanım açısından sınırlıdır. Gelecek çalışmaların şeffaf raporlama, özne düzeyinde doğrulama stratejileri, çok merkezli veri setleri ve açıklanabilir çok modlu modeller üzerine odaklanması, baş ağrısı pratiğinde yapay zekâ temelli araçların klinik güvenilirliğini artırmak açısından önem taşımaktadır.

Anahtar Kelimeler: Migren Bozuklukları, Sınıflandırma, Makine Öğrenmesi, Derin Öğrenme, Elektroensefalografi, Fonksiyonel Manyetik Rezonans Görüntüleme

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Introduction

Headache is a painful and disabling neurological disorder. According to the International Headache Classification System (ICHD), headaches are broadly classified into three main categories. The classification includes primary headaches such as migraine, tension-type headache and trigeminal autonomic cephalgia (or cluster headache), secondary headaches or facial pain, and painful cranial neuropathies (1). Migraine is a prevalent, chronic, and debilitating neurovascular disorder. It is characterised by episodic headaches and autonomic dysfunction (2). The occurrence of frequent headache attacks, neuropsychiatric problems and the risk of substance abuse, particularly opioid use, has a significant negative impact on the daily lives of patients when left untreated (3,4). In recent years, research has been conducted into the endogenous μ-opioid and D2/D3 dopamine systems to better understand the sensory and cognitive-motivational dysregulation observed in this disorder. These systems are targets of potent analgesic and antipsychotic drugs (5–7). A reduction in μ-opioid receptor (μOR) availability has been demonstrated in positron emission tomography (PET) studies in patients with migraine. This decrease was quantified using a radiotracer Carfentanil and was associated with increased endogenous opioid release. Additionally, increased D2/D3 dopamine receptor activity has been observed in the basal ganglia during migraine attacks. However, endogenous dopamine release was found to decrease with longer migraine history and higher attack frequency (8). Migraine patients also show a higher incidence of disorders associated with dopamine deficiency, such as Parkinson's disease and Restless Legs Syndrome (9,10). Over the past three decades, the global burden of migraine has increased substantially, contributing to a growing economic and societal impact (11,12).

Migraine is a categorised condition, with the following sub-types: migraine with aura (MWA), migraine without aura (MWoA) and chronic migraine. Approximately 25% of individuals diagnosed with migraine suffer from migraine with aura. MWA is characterised by the gradual onset of visual, speech and other central nervous system-related symptoms. The aura in migraine with aura typically lasts up to 60 minutes; per ICHD-3, each individual aura symptom usually persists for 5–60 minutes (1,13). In individuals experiencing migraines without aura, the headache is typically unilateral, throbbing, and moderate to severe in intensity. It impairs daily physical activity and is characterized by pain that interferes with or disrupts the individual's usual activities. In the absence of appropriate treatment, the pain may persist for up to 72 hours and is frequently accompanied by additional symptoms, including nausea, vomiting, phonophobia and photophobia (14). However, chronic migraine is defined as the recurrence of migraine in an individual with a minimum of 15 headache days per month, of which a minimum of eight are fully established migraine days (15). The pathophysiology of migraine is a complex and poorly understood phenomenon (16). The absence of specific biomarkers renders diagnosis largely dependent on the clinical presentation of symptoms. Over the past decade, there has been a notable increase in the number of studies investigating the specific biomarkers and pathogenesis of migraine. A substantial body of evidence indicates that the primary mechanism underlying migraine is the cerebral cortex (17).

From an AI perspective, the study of migraine pathophysiology is of particular interest due to the presence of measurable biomarkers in neuroimaging and EEG data, which are indicative of abnormalities in cortical excitability and functional network dynamics. Therefore, as opposed to examining the mechanisms in great detail, the present review concentrates on the practical implementation of these pathophysiological signatures as ML/DL features, with a view to enhancing diagnosis and subtyping classification (16,17).

Migraine diagnosis relies on identifying a combination of characteristic features, and it is relatively difficult to exclude possible causes, given the multiplicity of potential aetiologies. This renders the attainment of an accurate diagnosis through traditional methodologies, such as the analysis of symptoms or the performance of medical tests, a challenging endeavour. Indeed, the American Migraine Studies revealed that merely 65.2% of individuals experiencing migraine receive an accurate diagnosis (18). This diagnostic challenge highlights the necessity for the development of more reliable and efficient methods.

Recent developments in artificial intelligence (AI) have expanded its role in medical research and clinical decision support (19). AI-based methods are increasingly applied to analyse complex biomedical data, including neuroimaging and electrophysiological signals (20). In migraine research, these approaches provide computational tools to examine patterns that may not be readily detectable through conventional analytical techniques. Applications of AI in medicine include pattern recognition, risk prediction, treatment response

modelling, and biomarker exploration across neurological and related disorders (21,22). Broader strategic discussions have also emphasised the importance of responsible implementation, infrastructure development, and regulatory alignment to ensure safe and effective integration of AI technologies into healthcare systems (23).

At the core of AI, machine learning (ML) uses computational models that have the ability to automatically learn and improve from experience (24). Deep learning (DL) represents a subfield of ML that employs multi-level neural networks. A neural network is a model that employs multiple layers, which is indicated by the term "deep" (25). There is a need for an automated, affordable and accessible approach for migraine classification and prediction. Fortunately, ML and DL algorithms have been widely applied in various classification tasks, including text processing, speech recognition, and medical data analysis (26-28).

The objective of this review is to examine the applications of ML and DL methods in migraine research. In particular, it focuses on their role in migraine diagnosis and classification. The review aims to analyse the advantages and limitations of ML and DL techniques, including challenges related to dataset quality, accessibility, and clinical integration. It will also provide information on current challenges and future directions. The present manuscript was prepared as a structured narrative review. Rather than conducting a formal systematic review with predefined screening protocols, a concept-driven approach was adopted to summarise representative studies in the field. Relevant peer-reviewed articles were identified through targeted searches in PubMed and Google Scholar using combinations of keywords related to migraine, machine learning, deep learning, electroencephalography (EEG), magnetic resonance imaging (MRI/fMRI), positron emission tomography (PET), and classification. Studies were selected based on their relevance to migraine diagnosis or subtyping, methodological diversity, and the clarity of reported performance metrics and validation strategies. The aim was not to provide an exhaustive catalogue of all publications, but to critically synthesise prevailing methodological trends, reported performance ranges, and translational challenges.

Applications of Machine Learning in Migraine

Studying headache patients with ML methods may provide additional insights into migraine-related patterns. These methods have been used in neurological and psychiatric diseases such as Alzheimer's disease, depression and chronic pain disorders to help identify neuroimaging biomarkers that can predict clinical outcomes such as diagnosis, symptom severity, disease progression and response to treatment (29,30). ML approaches can be broadly categorized into two types: supervised and unsupervised. Supervised ML algorithms classify individuals into predefined categories, such as patients or healthy controls. These algorithms generate performance metrics that reflect their ability to generalise to new data (29,31). In this framework, the model learns discriminative features from labelled data and assigns new observations to one of the predefined groups (32). In contrast, unsupervised ML models are data-driven approaches that analyse datasets without predefined labels. The objective of this approach is to identify underlying structures or patterns within the data (32). These models generally comprise a training phase, during which patterns are learned from available data, followed by evaluation on independent observations.

Much of the recent ML work has been focused on the development of diagnostic tools for migraine. ML algorithms applied to resting brain fMRI or morphometric MRI data have identified brain features that differentiate migraine patients from healthy individuals (33–35). Functional connectivity in regions related to the emotional processing of pain distinguished migraine patients from controls with a reported accuracy of 86%. A higher level of classification performance was observed when comparing patients with a longer duration of the disease (>14 years) to those with a shorter disease duration. These findings suggest that disease duration may be associated with alterations in functional connectivity (33). Conversely, an unsupervised ML approach was unable to differentiate between migraine patients and healthy individuals based on brain morphometric measurements (35). Furthermore, a PET study utilising a semi-supervised ML approach reported classification accuracies ranging from 80% to 95% based on μ-opioid and dopamine receptor availability in pain-related brain regions (36). Nevertheless, these findings were derived from relatively small samples and require cautious interpretation.

Another area where ML is applied in migraine research is electroencephalography-based analysis for diagnostic classification and treatment monitoring. EEG signals are usually analysed in the temporal and frequency domains. Temporal features are defined as changes in brain activity over time, whereas frequency features reflect power distribution across bands such as alpha, beta, delta and theta (37). These features can be integrated with ML algorithms to support migraine classification. In a particular study, a Rotation Forest classifier distinguished migraine patients from healthy controls using subband features derived from EEG signals. Such approaches integrate multiple feature sets with a view to improving model performance (38).

A number of ML models have been developed to diagnose migraine using EEG data. The most commonly employed methodologies include support vector machines (SVM), random forest, and k-nearest neighbour (KNN) algorithms. SVMs are classification algorithms that identify an optimal hyperplane separating different data classes by maximising the margin between them. SVM is particularly effective in high-dimensional datasets and is capable of utilising kernel functions, such as the Radial Basis Function (RBF), to address non-linear classification problems. In migraine studies, SVM models have been applied to EEG features with reported high classification performance (39,40). The Random Forest is an ensemble learning method based on multiple decision trees trained on random subsets of the data. This structure can reduce overfitting and improve model stability. In EEG-based migraine classification, Random Forest models have been used to evaluate feature importance and classify migraine attacks (41,42). KNN is a distance-based algorithm in which new observations are classified according to the labels of their nearest neighbours. Unlike model-based approaches, KNN relies directly on stored training data during prediction. It has also been applied in EEG-based migraine classification (43). The reported performance of these algorithms varies depending on dataset size, signal quality, and preprocessing strategies. For example, one study reported 85% accuracy in classifying functional connectivity features derived from EEG data (44). Another study suggested that an SVM-RBF model could identify pre-ictal patterns prior to migraine onset (45). However, many of these studies are based on relatively small and homogeneous samples and rely primarily on cross-validation without independent external cohorts. This may lead to optimistic performance estimates and limit generalisability to broader clinical populations (46,47).

EEG-based ML approaches have also been used to differentiate migraine with aura from migraine without aura. In the study by Cao et al. (2018), an SVM-RBF classifier was applied to distinguish between these subtypes (45) Frid et al. (2020) reported that EEG functional connectivity measures contributed to subtype discrimination (44). These findings suggest that ML-based EEG analysis may help characterise neurophysiological differences between migraine subtypes, although further validation is required.

Applications of Deep Learning in Migraine

Deep learning has significantly influenced medical imaging by enabling advanced pattern recognition in complex neurological conditions such as migraine. Traditional diagnostic approaches often struggle to accurately classify migraine, with studies showing that only 65.2% of migraine patients are correctly diagnosed using standard clinical criteria (18). This diagnostic challenge has spurred the development of automated methods using DL techniques.

One notable application is the use of convolutional neural networks (CNNs) to analyse resting-state functional MRI (rs-fMRI) data. CNNs are a type of DL architecture designed to process image-based data using layered convolutional filters that automatically extract relevant features (48,49). In rs-fMRI analysis, CNNs can evaluate spatial and temporal patterns of brain activity associated with migraine (50,51). Features such as amplitude of low frequency fluctuations (ALFF), regional homogeneity (ReHo) and regional functional correlation strength (RFCS) have been used to differentiate migraine patients from healthy controls and to explore subtype differences between MWA and MWoA (52–54). ALFF measures the amplitude of low-frequency oscillations in specific brain regions within the 0.01–0.1 Hz range and reflects spontaneous neural activity (55). Altered ALFF values have been reported in migraine populations (56,57). ReHo quantifies the similarity of time series signals between neighbouring voxels and reflects local synchronisation of brain activity (58). Abnormalities in ReHo values in migraine patients may indicate alterations in functional connectivity within specific brain regions (59). RFCS assesses the strength of functional connectivity between brain regions and provides information about large-scale network interactions (60). Variations in RFCS have been associated with connectivity alterations in migraine (51,61). The research findings indicate that altered

connectivity in specific regions, including the prefrontal cortex and amygdala, may contribute to the underlying pathophysiology of migraines (52,53).

The application of advanced DL architectures, such as Inception module-based CNNs, has been associated with high reported classification performance. For instance, one study reported a maximum accuracy of 99.25% in differentiating individuals with migraine from healthy controls, compared with 83.67% reported for SVM-based models in the same dataset (62,63). These findings suggest potential performance advantages within specific experimental settings. Moreover, RFCS was identified as an informative feature for classification, reflecting alterations in global brain connectivity (53,64).

However, a considerable number of studies reporting near-perfect accuracies are based on limited sample sizes, frequently from single-center datasets, and rely on k-fold cross-validation without an independent validation cohort. This has been shown to increase the risk of overfitting and data leakage when multiple scans or EEG segments per subject are included (54,65,66). Consequently, reported performance may overestimate real-world diagnostic utility and should be interpreted with caution.

Deep learning frameworks also facilitate the differentiation of migraine subtypes. Patients with MWA have shown distinct functional connectivity patterns in regions such as the occipital cortex, which may relate to aura-associated mechanisms (67). These findings indicate that DL-based analyses may contribute to the characterisation of subtype-specific neural patterns.

Overall, DL approaches have expanded analytical capabilities in migraine research (62,63,67). However, their clinical translation requires larger, multi-centre datasets, rigorous external validation, and careful evaluation of generalisability. Before comparing ML and DL approaches, it is useful to summarise the key biomarkers and their reported diagnostic performance. Table 1 provides an overview of the principal features, data sources, and validation strategies described in ML/DL-based migraine studies.

It has been demonstrated that analogous ML/DL frameworks have been applied in other neurological disorders, including epilepsy and Alzheimer's disease (64,68–71). These research areas benefit from larger public datasets (e.g., ADNI, TUH-EEG), standardized acquisition protocols, and external benchmarking initiatives. These factors support more rigorous validation practices than are currently common in migraine research. The availability of such infrastructure and methodological standards may facilitate more robust development and validation of AI-based models in migraine.

Comparative Analysis of ML and DL Approaches

The application of ML and DL in migraine research presents a unique set of advantages and constraints. ML models, such as SVM and random forests, rely on domain-specific feature extraction, which enables clearer interpretation of variables such as spectral power and connectivity measures derived from EEG signals (65,72). This interpretability can support the exploration of underlying neurophysiological mechanisms in migraine. However, ML techniques may struggle to model complex hierarchical relationships in high-dimensional data, particularly in raw EEG recordings (46,65).

In contrast, DL models, including CNNs and recurrent neural networks (RNNs), are capable of automatically learning hierarchical features from raw data. This reduces the need for manual feature engineering (54,73). However, DL methods typically require larger datasets and greater computational resources, which can be limiting in migraine research where available datasets are often small and heterogeneous (45,47). Additionally, DL models are often criticized for their "black box" nature, which limits their interpretability compared to ML approaches (66,68).

The quality and availability of EEG data have a significant impact on the success of ML and DL applications in migraine research. EEG datasets are frequently limited in size, with considerable variability in recording protocols, electrode configurations, and patient demographics. These factors present a challenge to the development of generalisable models (46,74). Furthermore, EEG signals are frequently contaminated by noise and artefacts, requiring preprocessing techniques such as wavelet transforms and independent component analysis (ICA) to improve signal quality (46,65).

Table 1.

Comparison of Biomarkers and Their Diagnostic Utility

Biomarker	Source	Description	Utility in Migraine Diagnosis	ML/DL Methods	Accuracy	Sample Size (Approx.)	Validation Method	Disease Context	Key Limitations
ALFF	fMRI	Amplitude of low-frequency fluctuations in specific brain regions.	Indicates abnormal brain activity in migraineurs.	CNNs, RF	Reported high (85–90%, small single-centre cohorts)	n ≈ 30–60	k-fold CV	Migraine vs HC	Sensitivity to preprocessing; small samples.
ReHo	fMRI	Measures local synchronization of neural activity.	Highlights changes in connectivity patterns.	CNNs, SVM	Reported moderate (70–85%, cross-validated datasets)	n ≈ 40–80	5-fold CV	Migraine subtyping	Limited spatial specificity.
RFCS	fMRI	Strength of connectivity between specific brain regions.	Detects global connectivity changes in migraines.	Inception-CNNs	Reported high (95–99%, limited single-centre datasets)	n ≈ 45–60	Train/test split	Migraine vs HC	Risk of overfitting; needs external validation.
Temporal EEG Features	EEG	Changes in EEG waveforms over time.	Helps distinguish between migraine and healthy controls.	SVM, RotForest	Reported moderate (80–90%, cross-validated cohorts)	n ≈ 50–100	Cross-validation	Prodrome prediction	Susceptible to noise and artifacts.
Frequency EEG Features	EEG	Activity in different frequency bands (e.g., alpha, beta, theta).	Indicates abnormal electrical activity during migraines.	RF, SVM	Reported high (90–95%, subject-level CV; limited external validation)	n ≈ 60–120	Subject-level CV	Subtyping	Inter-subject variability.
μ-Opioid Receptor Availability	PET	Binding potential of μ-opioid receptors in pain-processing brain regions.	Differentiates between migraineurs and controls.	Semi-supervised ML	Reported moderate (80–95%, small exploratory samples)	n ≈ 15–25	Train/test	Migraine vs HC	Small sample sizes; cost and accessibility.

ALFF: Amplitude of Low-Frequency Fluctuations; ReHo: Regional Homogeneity; RFCS: Resting-State Functional Connectivity Strength; EEG: Electroencephalography; fMRI: Functional Magnetic Resonance Imaging; PET: Positron Emission Tomography; CNN: Convolutional Neural Network; Inception-CNN: Inception-based Convolutional Neural Network; RF: Random Forest; SVM: Support Vector Machine; RotForest: Rotation Forest; DL: Deep Learning; ML: Machine Learning; CV: Cross-Validation; k-fold CV: k-Fold Cross-Validation; HC: Healthy Controls; MWA: Migraine With Aura; MWoA: Migraine Without Aura; AI: Artificial Intelligence.

Interpretability remains a major challenge, particularly for DL models. Unlike many ML approaches, where feature importance can be directly examined, DL models operate in high-dimensional feature spaces that make decision processes less transparent. Methods such as saliency mapping and attention mechanisms have been proposed to improve interpretability (73,75). Beyond technical considerations, several barriers limit clinical integration of ML/DL models in migraine care. These include the need for rigorous external validation across diverse populations and healthcare settings to ensure generalisability (47). Regulatory pathways for AI-based medical devices continue to evolve and require substantial evidence of safety and effectiveness (76). Integration with Electronic Health Record (EHR) systems is necessary for real-time clinical use but remains technically complex (66). Furthermore, cost-effectiveness analyses are essential to determine the practical value of these technologies for healthcare systems (77).

The incorporation of ML and DL models into clinical workflows for migraine diagnosis and management is an area of ongoing investigation. Automated systems based on EEG data may assist clinicians in diagnosing migraine subtypes, predicting the onset of an attack, and monitoring the efficacy of a treatment plan. DL-based models have reported high performance in classifying migraine phases and detecting pre-ictal patterns, which could support earlier clinical intervention (44,73).

Nevertheless, clinical implementation requires rigorous validation across diverse patient populations and healthcare settings. The transparent reporting of performance metrics, including sensitivity, specificity, and area under the curve (AUC), is crucial for the establishment of trust and the assurance of reliability (47,78). Additionally, user-friendly interfaces and effective integration with electronic health records (EHRs) will be essential for enabling real-time decision-making (66).

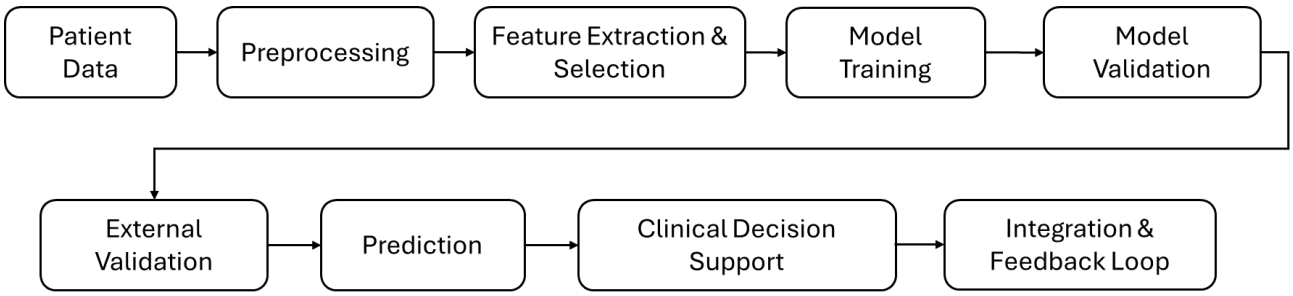


Figure 1. Schematic workflow for AI-based migraine diagnosis and clinical translation.

The general workflow for AI-based migraine diagnosis and its clinical translation is illustrated in Figure 1. The process begins with data collection, including neuroimaging (e.g., fMRI, PET), EEG recordings, and relevant clinical information. This is followed by preprocessing, such as noise reduction in EEG data and spatial normalisation of fMRI images. Feature extraction then involves measures such as ALFF and ReHo from fMRI, as well as temporal and frequency-domain features from EEG. Feature selection techniques, including statistical and ML-based methods, are applied to reduce dimensionality and identify informative diagnostic variables. ML/DL algorithms (e.g., SVM, Random Forest, CNN, deep neural networks) are then trained on labelled datasets (e.g. migraine vs. healthy control). Model validation includes evaluation on separate test data using performance metrics such as accuracy, sensitivity, and specificity. External validation across independent, multi-centre datasets is recommended to assess reproducibility and generalisability under varying protocols and demographic conditions. Once validated, the model can be deployed to classify new cases, predict migraine subtypes, or forecast migraine onset. In clinical practice, model predictions must be accompanied by performance uncertainty estimates (e.g., confidence intervals) and explainability tools such as saliency maps or attention heatmaps. Post-deployment monitoring and periodic recalibration are important to maintain model stability as new data become available (79). This iterative process supports safer and more scalable integration of AI tools into headache care pathways.

Research in migraine ML/DL remains heterogeneous in terms of study design, sample size, and validation strategy. Many studies have relied on cross-validation without strict subject-level separation, increasing the risk of information leakage when multiple samples originate from the same individual (46,54,65). Robust study

design includes clearly defined inclusion criteria, balanced group allocation, subject-level data partitioning, and, when possible, independent external test cohorts to strengthen generalisability (35,47,66). Transparent reporting of preprocessing steps, model parameters, and evaluation metrics beyond accuracy (e.g., AUC, sensitivity, specificity) is required to ensure reproducibility (66,73).

Table 2.
Recommended Reporting Standards for Migraine ML/DL Studies

- ✓ Subject-level train/validation/test splits should be applied to avoid data leakage when multiple samples per subject exist.
- ✓ Nested cross-validation is employed when tuning model hyperparameters.
- ✓ Independent external test cohorts should be used whenever possible to improve clinical generalizability.
- ✓ Performance reporting should encompass not only accuracy but also AUC, sensitivity and specificity, and confidence intervals.
- ✓ Preprocessing steps, feature extraction methods, and model parameters should be documented with transparency.
- ✓ Sharing of code and, where feasible, de-identified data is encouraged to enhance reproducibility.
- ✓ Multi-centre recruitment and harmonized acquisition protocols are recommended to better represent real-world migraine populations.

Several recent systematic reviews have examined the application of AI in headache disorders (80,81). These reviews consistently report two main findings: AI-based approaches show potential for improving diagnostic classification, yet persistent methodological limitations continue to restrict clinical translation. Common concerns include small sample sizes, limited external validation, heterogeneous preprocessing strategies, and insufficient reporting transparency. Addressing these limitations remains essential for strengthening the evidence base and supporting responsible implementation in clinical practice.

Conclusion

The incorporation of ML and DL methodologies in migraine research has expanded analytical approaches to this complex disorder. These computational methods have shown potential in improving diagnostic classification, exploring candidate biomarkers, and supporting personalised management strategies (29,55). By analysing neuroimaging modalities such as fMRI and EEG, researchers have gained additional insight into functional and structural alterations associated with migraine (52).

ML techniques, including SVM, random forests, and KNN algorithms, have been applied to structured features extracted from neuroimaging and EEG data (39,41,45). These approaches have been used to differentiate migraine patients from healthy controls and to explore subtype classification, including MWA and MWoA. The integration of temporal and frequency-domain EEG features with ML models has also been investigated for attack prediction and treatment monitoring.

DL models, including CNNs and recurrent neural networks (RNNs), enable hierarchical feature learning from high-dimensional data (62,63). CNN-based analyses of resting-state fMRI have identified alterations in functional connectivity and regional brain activity in migraine populations. Although some studies report very high classification performance, including accuracies exceeding 99% in specific datasets, such findings should be interpreted cautiously given limitations related to sample size, validation strategy, and potential overfitting (62).

Despite these developments, considerable obstacles remain. Variability in data quality and limited access to large, standardised datasets constrain model generalisability. Differences in acquisition protocols, electrode

configurations, and demographic characteristics introduce heterogeneity that may affect reproducibility. The limited interpretability of DL models also remains a barrier to clinical adoption. Addressing these issues will require improved reporting standards, explainable AI frameworks, and validation across diverse populations.

Regulatory and health-system considerations further influence clinical translation. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require robust evidence of safety, effectiveness, and clinical benefit prior to approval of AI-based tools (82,83). External validation across ethnically and demographically diverse populations is necessary to minimise bias (84). Integration with electronic health records (EHRs) and clinical decision-support systems remains technically complex due to interoperability and data governance challenges (85). In addition, cost-effectiveness analyses are needed to support adoption within healthcare systems (11,86).

Multimodal approaches combining EEG with other imaging modalities, including MRI and PET, may offer complementary structural, functional, and metabolic information. Interdisciplinary collaboration between neurologists, data scientists, and engineers will be essential to ensure that computational models address clinically relevant questions. Lessons from AI applications in other neurological disorders, such as epilepsy and Alzheimer's disease, may also inform methodological development in migraine research (87).

Overall, ML and DL approaches provide valuable analytical tools for investigating migraine-related biomarkers and classification strategies. However, their clinical impact will depend on rigorous validation, transparent reporting, larger multi-centre datasets, and careful integration into existing healthcare systems. Continued methodological refinement, rather than technological optimism alone, will determine their role in future migraine care.

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