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Advanced EEG-based learning approaches to predict schizophrenia: Promises and pitfalls

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ABSTRACT

The complexity and heterogeneity of schizophrenia symptoms challenge an objective diagnosis, which is typically based on behavioral and clinical manifestations. Moreover, the boundaries of schizophrenia are not precisely demarcated from other nosologic categories, such as bipolar disorder. The early detection of schizophrenia can lead to a more effective treatment, improving patients' quality of life. Over the last decades, hundreds of studies aimed at specifying the neurobiological mechanisms that underpin clinical manifestations of schizophrenia, using techniques such as electroencephalography (EEG). Changes in event-related potentials of the EEG have been associated with sensory and cognitive deficits and proposed as biomarkers of schizophrenia. Besides contributing to a more effective diagnosis, biomarkers can be crucial to schizophrenia onset prediction and prognosis. However, any proposed biomarker requires substantial clinical research to prove its validity and cost-effectiveness. Fueled by developments in computational neuroscience, automatic classification of schizophrenia at different stages (prodromal, first episode, chronic) has been attempted, using brain imaging pattern recognition methods to capture differences in functional brain activity. Advanced learning techniques have been studied for this purpose, with promising results. This review provides an overview of recent machine learning-based methods for schizophrenia classification using EEG data, discussing their potentialities and limitations. This review is intended to serve as a starting point for future developments of effective EEG-based models that might predict the onset of schizophrenia, identify subjects at high-risk of psychosis conversion or differentiate schizophrenia from other disorders, promoting more effective early interventions.

1. Introduction

Schizophrenia (SZ) is a chronic and complex neuropsychiatric disorder, with an estimated prevalence of 1% worldwide [1]. Its onset typically occurs by the end of adolescence and beginning of early adulthood [2]. SZ symptoms are heterogeneous and associated with functional impairments and reduced quality of life [3], being one of the top 25 leading causes of disability worldwide [4,5]. SZ is characterized by the presence of positive (e.g., hallucinations and delusions) and negative symptoms (e.g., blunted affect), as well as cognitive deficits [6]. Functional impairment has been consistently correlated with changes in cognitive functions [6], including attention, memory, language, and executive functions [7,8], which are already observed before illness onset [9,10].

Psychotic symptoms such as hallucinations and delusions are not exclusive of SZ [11] but might be present in other psychiatric (e.g., bipolar disorder [12]) or neurological (e.g., temporal lobe epilepsy [13]) disorders. Additionally, psychotic-like experiences have been reported in healthy subjects without a need for clinical care [14], supporting the notion that psychotic symptoms exist on a continuum in the general population [15–19]. Evidence for a psychosis continuum challenges the binary categorization of psychotic disorders, with implications for clinical diagnosis. A dimensional approach to psychosis may provide critical insights on risk factors for psychosis, disease progression, and prognosis [17]. In particular, identification of risk factors is imperative to prevent or delay disease onset [20]. For example, early interventions could reduce the negative impact of SZ [21]. However, the lack of reliable methods to objectively define the onset of psychiatric disorders

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hampers the precise diagnosis of SZ [22].

Several research teams worldwide are committed to shed light on the neurobiological mechanisms underpinning the clinical manifestations of SZ, which may lead to substantial improvements in diagnosis and prognosis [23]. Advances in neuroscience methodologies have fostered the study of this complex disorder. Studies using functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) or electroencephalography (EEG) have identified changes in brain structure and function associated with sensory and cognitive abnormalities in SZ [24–26]. Given its high temporal resolution (in the order of milliseconds), the EEG technique can capture the brain dynamics underpinning sensory, cognitive, affective and/or motor processes in response to a stimulus [27,28]. Furthermore, it is an affordable method to directly measure cortical brain activity [27]. Machine learning applied to EEG data might represent a promising contribution to the accurate prediction of intervention response and disease trajectories [29]. Machine learning methods could enhance our understanding of the brain mechanisms underlying SZ by contributing to three key domains: diagnosis and detection; prognosis and onset prediction; biomarker identification.

The current paper provides a systematic review of studies that relied on advanced learning methods to detect SZ based on EEG signals. Specifically, it aims to provide an overview of proposed neurophysiological biomarkers in SZ research, as well as a critical analysis of machine learning methods applied to EEG data for SZ classification since 2016, further specifying deep learning methods used for the same purpose. Moreover, it aims to identify and evaluate the potentialities and limitations of both types of learning methods.

2. Search strategy and inclusion criteria

A literature search of studies that applied machine learning methods on EEG data for SZ classification, published from January 2016 until April 2020, was conducted using *SCOPUS*, *PubMed*, *Google Scholar*, *IEEE Xplore*, and *ArXiv* databases, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [30]. Advanced search terms included the following keywords: "*EEG or electroencephalography*", "*schizophrenia*", and "*machine learning*". Studies were included if (1) they aimed to discriminate SZ and/or at-risk patients from healthy control (HC) subjects or from patients with other psychiatric disorders; (2) they used machine learning techniques applied to EEG data. Only studies published after 2016 were considered to allow a clearer view on the trends and improvements observed in this research field in the last 5 years. A total of 26 studies were included in the current review (Fig. 1).

3. SZ diagnosis

The complex nature of SZ and the controversy concerning its delimitation from other psychiatric disorders represent challenges to an objective clinical diagnosis [31]. Currently, SZ diagnosis mostly relies on the assessment of behavioral manifestations of clinical symptoms and on self-reports of subjective experience. Since SZ shares symptomatic features with other disorders, diagnosis may not be straightforward [32]. Specific tools have been developed to aid diagnosis: the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatry Association (APA) [33], and the International Statistical Classification of Diseases (ICD-10), published by the World Health Organization (WHO) [34], list criteria for the classification of psychotic disorders. Adjustments in both systems over time have been based on robust phenomenological studies [32]. Nevertheless, DSM-5 and ICD-10 have not been able to merge neurobiological evidence with clinical diagnostic criteria, mainly because brain and behavioral data do not properly map onto current symptom-based disorders [35,36]. The Research Domain Criteria (RDoC), a National Institute of Mental Health (NIMH) project [37,38], aims to integrate basic behavioral and neuroscience research to understand the core mechanisms underpinning symptoms that may span multiple disorders [29,39]. Despite the improved reliability, both DSM-5 and ICD-10 diagnostic systems are limited by human subjectivity [39].

4. Neurobiological changes in SZ

The neurobiological mechanisms underpinning SZ symptoms have been studied for decades with neuroimaging techniques, such as MRI, fMRI, MEG or EEG. These methods directly or indirectly provide information on structural or functional brain changes in the disorder. Each has advantages and disadvantages, mainly associated with its capacity to find the source of a particular brain signal and to distinguish two brain structures next to each other in space (spatial resolution), as well as with its capacity to discriminate two sequential events in time (temporal resolution) [40]. Whereas MRI and fMRI are characterized by higher spatial resolution, MEG and EEG have higher temporal resolution [41].

Structural and functional brain alterations have been consistently documented in patients diagnosed with SZ [42], which include a reduction of gray matter volumes in medial temporal, superior

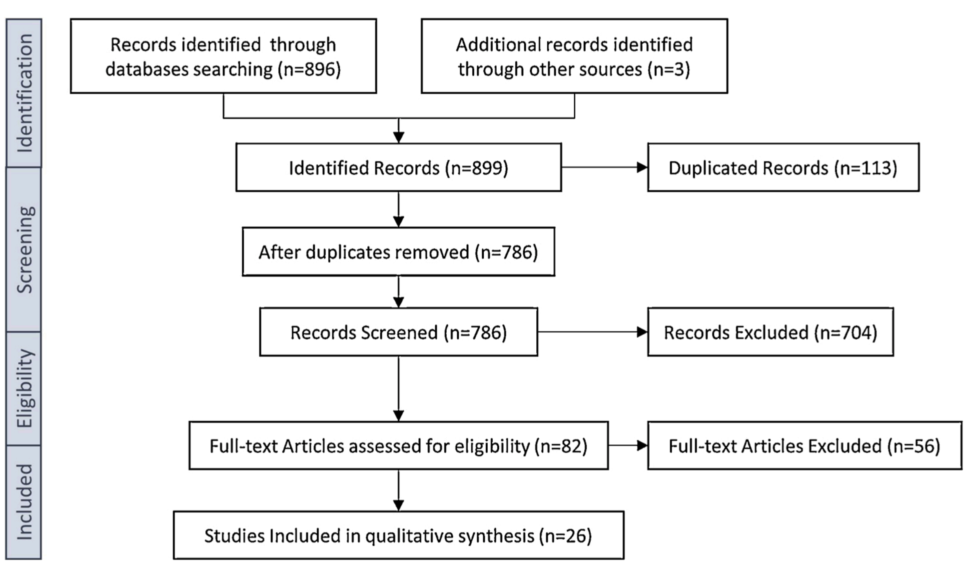

Fig. 1. PRISMA flow diagram of the systematic literature search.

temporal, and prefrontal areas [43–45]. These brain regions are engaged in episodic memory, auditory processing, and short-term memory/decision making, respectively [42,43].

Although the clinical symptoms and course of the disorder are heterogeneous, cognitive deficits are a central feature of SZ and include changes in executive functioning, attention, and working memory [46–49]. Cognitive dysfunction may precede the onset of psychosis, is related to functional outcome, and little influenced by antipsychotic treatment [46,50]. Inadequate reception, discrimination, integration, or modulation of sensory information can affect higher-order cognitive processes [51,52]. fMRI provides a powerful method to explore the neural circuitry underlying cognitive deficits in SZ. These abnormalities are manifested in dysconnectivity between brain regions, as well as in changes in task-related brain activation [42,45,53–56]. Despite its high spatial resolution, the fMRI technique has low temporal resolution (in the order of seconds). The exquisite temporal resolution of EEG, in the order of milliseconds, and its relatively low cost compared to the MEG technique are ideal to investigate how changes in information processing contribute to perceptual, cognitive, and social impairments in SZ [27,57].

5. Electrophysiological biomarkers of SZ

A great challenge to clinical research is the identification of biomarkers to aid diagnosis, prognosis, risk stratification or treatment monitoring of SZ [58–63]. Specifically, the identification of biomarkers may shed light on the biological underpinnings of different categorically defined disorders [36]. Combined with technological advances, neuroimaging techniques have enabled the identification of psychosis-related neurobiological changes that are considered markers of psychopathology. Many of the proposed SZ biomarkers are EEG-related indices. The temporal resolution of EEG is ideal to investigate how changes in information processing contribute to sensory, cognitive, and social impairments in SZ [27,28]. Several experimental paradigms have been designed to probe differences between SZ patients and healthy control subjects [64]. Consistent changes in specific event-related potential (ERP) components have been proposed as trait markers of SZ (Table 1) [65,66].

The predictive value of a biomarker depends on its generalizability across clinical populations, as well as on its sensitivity and specificity for a target population [90]. Recently, the ERP Biomarker Qualification Consortium (LLC [91]) was launched to identify ERP biomarkers of SZ. Accordingly, a broad range of classification and predictive models may be developed [61].

6. Machine learning for detection and prediction of SZ

Machine learning methods have been increasingly adopted to optimize the use of neurobiological data in classification tasks and development of predictive models. Through the combination of computational science and statistics, machine learning methods assess and automatically identify data patterns, and use those recognized patterns to make predictions [92]. As the human brain learns from experience, machine learning algorithms also learn from data. Data examples are represented as vectors of features [93], which can be manually or automatically extracted and selected, and are expected to contain relevant information to effectively train the model as input to a learning phase [94].

The learning process can be classified as supervised, unsupervised, and semi-supervised, based on the data and analyses to be conducted [95]. In supervised learning, a target vector (label) is provided for each data example expressing its category [93,94]. During the learning phase, a relationship between a label and the input features is determined, allowing the model to accurately categorize or predict classes for new data, i.e., to generalize [94]. Contrarily, the unsupervised learning can infer patterns from non-categorized data based on the underlying structure [92,95]. The principal component analysis (PCA) and clustering are examples of unsupervised methods [93]. Semi-supervised methods aim to overcome the huge amount of data needed in supervised learning and the cost of labelled data acquisition. Semi-supervised algorithms are applied to a small amount of labelled data augmented by larger unlabeled datasets [96,97]. Table 2 presents the list of acronyms and abbreviations used to identify the machine learning algorithms hereinafter described or reported.

6.1. Classical machine learning approaches

Machine learning methods used in psychiatry research and,

Table 2
List of acronyms and abbreviations used to identify machine learning algorithms.

ANN	Artificial neural network	PCA	Principal component analysis
CNN	Convolutional neural network	PNN	Probabilistic neural network
DT	Decision tree	QDA	Quadratic discriminant analysis
FFNN	Feed-forward neural network	RF	Random forest
GPC	Gaussian process classifier	RNN	Recurrent neural network
kNN	k-nearest neighbors	SNN	Siamese neural network
LDA	Linear discriminant analysis	SVM	Support vector machine
LRA	Logistic regression analysis	SVM-poly	SVM with a polynomial function kernel
MLP	Multi-layer perceptron	SVM-RBF	SVM with radial basis function kernel
NB	Naïve bayes	XGBoost	Extreme gradient boosting

Table 1
Examples of proposed EEG biomarkers of SZ.

Proposed Biomarker	Type of feature	Functional Significance	Task	Amplitude	Latency	Power	Phase	References
Mismatch Negativity (MMN)	ERP component	Pre-attentive deviance detection	Auditory oddball paradigm	SZ<HC	–	–	–	[67–70]
P300	ERP component	Attention allocation	Auditory oddball paradigm	SZ<HC	SZ>HC	–	–	[70–76]
P50	ERP component	Sensory gating	Paired-click paradigm	SZ<HC	–	–	–	[70,77]
N100 (N1)	ERP component	Early auditory response, sensory and perceptual processing	Listening paradigm	SZ<HC	–	–	–	[78–81]
Gamma Band (30–80 Hz)	Brain oscillation	Selective attention; complex auditory information processing	Auditory oddball paradigm	–	–	SZ<HC	SZ<HC	[82–85]
40 Hz Auditory Steady-State Response (ASSR)	Brain oscillation	Sensory response; integrity of auditory circuits; synchronization of neural activity with external stimuli	Listening paradigm	–	–	SZ<HC	SZ<HC	[86–89]

specifically, in SZ have mostly relied on supervised learning models, trained with quantitative features selected and extracted from specific input data [98–100]. Following the training phase, a classification task is performed, in which test data are categorized [93,99,101].

SZ classification using features extracted from EEG data has been tested for several years [102–109]. Table 3 summarizes the latest machine learning-based classification studies conducted since 2016, grouped according to classification goal and EEG task . Most recent studies relied on auditory, visual or working memory tasks, which tap into perceptual and cognitive processes that are altered in SZ, aiming to differentiate SZ from HC and at-risk subjects, as well as from other psychiatric disorders. Additionally, some approaches focused on resting-state EEG data, allowing the evaluation of intrinsic (i.e., task-unrelated) neural activity. Information on subject-dependence classification is also presented for each study in Table 3. In a subject-independent evaluation, the model is tested using unseen subjects' data, i.e., the subjects' data used to test the model are not included in the training phase. On the contrary, in a subject-dependent classification training and testing sets are randomly split, and data from the same subject are included in both sets.

6.1.1. *Classification of SZ and healthy subjects*

Fig. 2 graphically summarizes the methods tested for the binary classification of SZ and the best performance of the proposed methods for specific tasks and groups of features.

6.1.1.1. Visual processing. Recent studies have focused on event-related potentials (ERPs) elicited during visual tasks. Devia *et al.* [116] examined differences between SZ and HC subjects in a simple visual task. Mean ERP amplitude in the 400−600 ms temporal window post-stimulus onset, averaged across four regions of interest (frontal, central, parietal, and occipital), was used as machine learning feature. Three classifiers were tested: LDA, a rule-based, and a combination of the posterior probability of two LDAs. The rule-based and the LDA classifiers using occipital ERPs in response to landscape images obtained the best performances (71 % accuracy) [116]. Li and colleagues [118] examined features of signals recorded during task (P300) and rest conditions. Additionally, the functional network of both rest and task brain states was examined by computing the phase-locking value, reflecting phase synchronization between electrodes [130]. Using spatial pattern analysis (SPN), properties of both networks were extracted. The features from both states were combined allowing a highly accurate (90.48 %) identification of SZ patients with a SVM classifier [118]. Similarly, Thilakvathi *et al.* [117] combined features of visual oddball tasks and resting-state EEG signals. The classification was performed using FFNN and SVM algorithms using six entropy and complexity-related parameters from each condition. Unlike the findings of Li *et al.*, the combination did not improve the accuracy achieved by the visual task features alone (88.5 %), as shown in Fig. 3.

6.1.1.2. Auditory change detection. Auditory tasks have also been the focus of SZ binary classification with machine learning. Shim *et al.* [111] relied on an auditory oddball task (AOT), combining sensor- (i.e., P300 peak over 62 electrodes) and source-level (i.e., cortical current density) approaches. The SVM classifier with 15 features combining eight sensor-level (over frontal electrodes) and seven source-level features (over the left temporal cortex) achieved the best accuracy (88.24 %). This result is consistent with reported P300 changes in SZ [111]. Santos-Mayo *et al.* [112] used an AOT with three types of auditory stimuli (standard, target, and distractor) to elicit the P300. Features in both time and frequency domains were extracted and examined across different electrode clusters. The SVM algorithm resulted in a highly accurate SZ classification (92.23 %), considering right hemisphere electrodes only; a MLP was tested using all electrodes achieving an accuracy of 93.42 %. Taylor *et al.* [113] probed the MMN using three AOT with different types of deviants (stimulus duration, presence of right or left monaural gap, interaural time). ERP data were converted into spatiotemporal images (two-dimensional surface of the scalp over the timepoints) for each deviant and fed into two classifiers: SVM and GPC. The best achieved accuracy was of 80.48 % using GPC, with no significant differences between both classifiers [113]. Probing the processing of musical sounds, Hsieh *et al.* [114] reported decreased N1 and P2 amplitudes over frontal electrodes in SZ subjects, used as features in a LDA classifier. This classifier discriminated SZ and HC subjects with an accuracy of 83.3 % [114]. Zhang *et al.* [115] also tested SZ classification based on N1 and P2 features associated with three conditions: a button-press task to generate a tone (*press* + *audio*); the passive listening of the same tone (*audio*); the button-press without sound (*press*). Using RF algorithms, the best accuracy (81.10 %) was achieved when N1 amplitude and latency over Fz from *button-press* + *audio* and *audio* conditions were combined with non-ERP related features (demographic data).

Despite the variety of features extracted, the reviewed studies show that AOTs contribute to an accurate identification of SZ patients. Specifically, the high accuracy in tasks eliciting the P300 or MMN supports the reliability of changes in these components and their contribution to SZ classification. Of note, the combination of both time and frequency domains features led to improved accuracy. Data from small groups of electrodes enhanced the classifiers' performance when compared to EEG activity distributed over the entire scalp.

6.1.1.3. Working memory. EEG signal decomposition into specific frequency bands allows probing neural oscillatory activity. Johannesen *et al.* [110] examined EEG time-frequency measures using a Sternberg Working Memory Task (SWMT), focusing on event-related spectral perturbations (ERSP) in theta (θ – 3−8 Hz), alpha (α – 8−14 Hz), beta (β – 14−23 Hz), and gamma (γ – 30−50 Hz) bands. Performance was specified using those bands over different time intervals (pre-stimulus baseline, encoding, retention, and retrieval stages) and three scalp locations (frontal [Fz]; central [Cz]; and occipital [Oz]). SZ patients were identified with an accuracy of 87 % using the SVM classifier. Specifically, gamma activity during the encoding interval was the main feature contributing to this outcome [110].

6.1.1.4. Resting-state. Considering the documented resting-state EEG alterations in SZ [131], classification based on task-unrelated features has been also examined. Sabeti and Boostani [120] decomposed the resting-state signal into five frequency bands (delta, theta, alpha, beta, and gamma) across 24 electrodes, using discrete wavelet transforms, and computed the average power of each band. The most discriminative frequency band was selected and its features fed into a LDA classifier, achieving the highest accuracy (83.74 %) [120]. Piryatinska *et al.* [119] extracted ε-complexity (indexing signal's complexity [132]). The model was tested on simulated data and applied to the binary classification of EEG recordings, using SVM and RF algorithms. The best performance was a mean accuracy of 85.3 % using the RF classifier [119].

Using the same EEG database, three other studies also probed SZ classification [121–123]. Jahmunah *et al.* [121] and Goshvapour and Goshvarpour [123] selected entropy and complexity measures as classifier features. Jahmunah *et al.* [121] achieved the highest accuracy of 92.91 % using the SVM-RBF with 12 features. SVM-poly, PNN, RF, DT, kNN, and LDA were also tested, with accuracies, sensitivities, and specificities above 78 % [121]. Goshvapour and Goshvapour [123] implemented a PNN model using only three features and testing different combination rules. The perfect classification (100 % accuracy) was obtained using a feature-level fusion method [123]. Buettner *et al.* [122] decomposed the EEG data into 99 frequency values (from 0.5–50 Hz), and accurately (71.43 %) classified SZ using a RF; 16 Hz, 41 Hz, and 49 Hz frequencies contributed more significantly to the performance [122].

Table 3
SZ classification attempts using classical machine learning methods based on the EEG signal. The selected studies were categorized according to classification task and EEG paradigm.

Classification Task	Paradigm	Author [Reference]	Year	EEG channels	Sample Size	EEG Task	Classifier	Features	Evaluation Method (Train/Validation/ Test)	Test set size	Accuracy*
	Working memory	Johannesen [110]	2016	64	12 HC; 40 SZ	SWMT	SVM	Event-related spectral perturbations	3-fold cross-validation (66 % / - / 33 %)	12 HC; 40 SZ ⊗	87 %
		Shim [111]	2016	62	34 HC; 34 SZ	Simple AOT	SVM	P300 peak amplitude and latency; cortical current density values	Leave-one-out cross-validation	34 HC; 34 SZ ∅	88.24 %
		Santos-Mayo [112]	2017	17	16 HC; 31 SZ	AOT (standard, target, distractor)	SVM, MLP	P3b time-domain features; frequency-domain features	(60 %/10 %/30 %)	14 subjects (not balanced) ⊗	93.42 %
	Auditory Processing	Taylor [113]	2017	32	22 HC; 21 SZ	AOT (3 tasks, 3 different deviants)	SVM, GPC	Spatiotemporal images of MMN, deviant and standard responses	10-fold cross-validation (90 % / - / 10 %)	22 HC; 21 SZ ⊗	80.48 %
		Hsieh [114]	2018	32	12 HC; 12 SZ	Passive listening	LDA	N1 and P2 peak amplitudes	Leave-one-out cross-validation	12 HC; 12 SZ ⊗	83.3 %
		Zhang [115]	2019	64	32 HC; 49 SZ	Basic sensory tasks with button press and auditory tone	RF	Demographic data; amplitude and latency of N1 and P2 peak.	10-fold cross-validation (90 % / - / 10 %)	32 HC; 49 SZ ∅	81 %
SZ vs. HCSZ vs. HC	Visual Processing	Devia [116]	2019	32	9 HC; 11 SZ	Simple visual-free task	Rule-based, LDA	Amplitude of ERP signals	5-fold cross-validation (80 % / - / 20 %)	9 HC; 11 SZ ⊗	71 %
	Visual Processing + Resting-state	Thilakvathi [117]	2017	23	23 HC; 55 SZ	Modified visual oddball, Resting-state	FFNN, SVM	Entropy and complexity measures	(80 % / - / 20 %)	3 HC; 15 SZ ⊗	88.5 %
		Li [118]	2019	16	25 HC; 23 SZ	Resting-state; Visual P300 task	LDA, SVM	P300 amplitudes SPN features	Leave-one-out cross-validation	25 HC; 23 SZ ⊗	90.48 %
		Piryatinska [119]	2017	16	39 HC; 45 SZ	Resting-state	RF, SVM	ε-complexity	10-fold cross-validation (90 % / - / 10 %)	39 HC; 45 SZ ⊗	85.3 %
		Sabeti [120]	2018	24	20 HC; 20 SZ	Resting-state	LDA	Average power of frequency bands	10-fold cross-validation (90 % / 10 % / -)**	10 HC;10 SZ ⊗	83.74 %
	Resting-StateResting-State	Jahmunah [121]	2019	19	14 HC; 14 SZ	Resting-state	SVM-RBF, SVM-poly, DT, LDA, kNN, PNN	Entropy and complexity measures	N.A.	14 HC; 14 SZ ⊕	92.91 %
		Buettner [122]	2019	19	14 HC; 14 SZ	Resting-state	RF	frequency bands power	10-fold cross-validation (90 % / 10 % / -)**	2 HC; 5 SZ ⊗	71.43 %
		Goshvarpour [123]	2020	19	14 HC; 14 SZ	Resting-state	PNN	Entropy and complexity measures	5-fold cross-validation (80 % / - / 20 %)	14 HC; 14 SZ ⊕	100 %
	Resting-state	Ye [124]	2017	64	40 HC; 40 FES; 40 CHR	Resting-state	SVM, kNN	Statistics and Linear Eigenvalue Statistics	(75 % / - / 25 %)	10 HC; 10 FES; 10 CHR ⊗	97.50 % [a]; 77.33% [b]
		Liu [125]	2018	64	40 HC; 40 FES; 40 CHR	Resting-state	SVM, RF, NB, DT	Statistics and Linear Eigenvalue Statistics	5-fold cross-validation (80 % / - / 20 %)	40 HC; 40 FES; 40 CHR ⊗	91.16 % [a] 73.31% [b]
HC vs. ‘at risk’ vs. SZ		Luo [126]	2019	128	44 FES; 34 UHR; 19 CHR; 39 HC	Somatosensory P50 suppression	XGBoost	P50 amplitudes and P50 suppression ratio; behavioural data	(70 % / - / 30 %)	40 subjects (not balanced) ∅	90.2 % [c]
	Auditory Processing	Chang [127]	2019	128	25 FES; 23 UHR; 19 HC	P50 paradigm	DT	ERP measures, MCCB, brain network properties, demographic data	5-fold cross-validation (80 % / - / 20 %)	25 FES; 23 UHR; 19 HC ⊗	77.80 % [b]
		Ahmedt-Aristizabal [128]	2020	30	40 HC; 65 RSz	Passive auditory oddball	KNN, SVM, DT	Early and mid-latency ERP amplitudes	5-fold cross-validation (64 % / 16 % / 20 %)	40 HC; 65 RSZ ⊗	44.75 %

(*continued on next page*)

Table 3 (*continued*)

Classification Task	Paradigm	Author [Reference]	Year	EEG channels	Sample Size	EEG Task	Classifier	Features	Evaluation Method (Train/Validation/Test)	Test set size	Accuracy*
SZ vs. Other disorders	Visual Processing	Alimardani [129]	2018	21	23 BD; 23 SZ	SSVEP	LDA, QDA, SVM, kNN, LRA	SNR mean, skewness, and kurtosis	Leave-one-out cross-validation	23 BD; 23 SZ ⊗	91.30 %

*Concerning the method with the best performance (bold in the *Classifier* column) **used an independent test set [a]HC vs. FES [b]Three groups comparison [c]Four groups comparison.
⊗ subject-independent evaluation ⊕ subject-dependent evaluation ∅ subject-dependency level not specified.
Abbreviations: **EEG**Electroencephalography; **HC** Healthy Control; **SZ**Schizophrenia; **BD**Bipolar Disorder; **FES**First-Episode in Schizophrenia; **CHR**Clinical high-risk; **UHR**Ultra-high-risk; **RSz**At-risk of developing Schizophrenia; **SWMT**Sternberg Working Memory Task; **SSVEP** Steady State Visually Evoked Potential; **MMN**Mismatch Negativity; **SNR** Signal-to-Noise Ratio.

The lack of task-related elements in the resting-state signal may hinder feature engineering. Notwithstanding, accurate classification of SZ was achieved using frequency decomposition and signal complexity approaches. Performance was improved when a combination of task-related and resting-state features was used [118].

6.1.2. *From risk to disease progression*

Changes in brain structure and function observed before SZ onset support the role of neurodevelopmental abnormalities in this disorder [21]. Studying different SZ stages (e.g., prodromal, first episode, chronic stage) may specify the pathophysiological mechanisms underpinning the disorder and provide important clues to outcome and prognosis. Some (although few) studies relied on machine learning algorithms to discriminate stages of SZ progression. Luo *et al.* [126] and Chang *et al.* [127] examined the role of the auditory P50 as a potential biomarker for detection of psychosis risk. Both studies used the amplitude and suppression ratio as input features. Luo *et al.* [126] applied the XGBoost to classify HC, clinical high-risk (CHR), ultra-high-risk (UHR) subjects, and first episode (FES) patients. Groups were classified with an average accuracy of 90.2 % based on EEG and behavioral data [126]. Chang *et al.* [127] used DT algorithms to discriminate HC, UHR, and FES. Demographic data, cognitive performance data, and brain network parameters were combined with P50 measures, resulting in an accuracy of 77.80 %. Liu *et al.* [125] recorded data from HC, CHR, and FES, and tested different classifiers, relying on statistical measures of the signal (e.g., standard deviation, kurtosis, root mean square) and linear Eigenvalue statistics (LES). The best accuracy (approximately 91 %) was achieved in the binary discrimination of HC and FES, using LES features with SVM. Discrimination of the three groups was achieved with a 73.31 % accuracy using the same approach [125]. Likewise, Ye *et al.* [124] probed the role of different frequency bands in the discrimination of the same groups. Delta, theta, and low gamma frequencies played a more relevant role in the binary classification of HC and FES (97.50 % accuracy), whereas alpha, beta and mid-range gamma bands were more relevant to the discrimination of the three groups (77.3 % accuracy). The classification focused on LES features extracted from those specific bands.

Compared to the high accuracy obtained in FES−HC discrimination, machine learning algorithms were less accurate when performing multi-groups classification using resting-state signals. Studies focusing on the SZ prodromal phase may provide insights into the EEG features that differ between control, at-risk, and diagnosed subjects. Of note, the use of auditory task-related signals showed improved accuracy, though combined with features such as demographic or behavioral data.

Ahmedt-Aristizabal *et al.* [128] implemented machine learning methods to identify children at-risk of developing SZ, comparing 65 at-risk subjects (RSz) with a control group of 40 participants, with ages between 9 and 12 years. At-risk children presented psychotic-like experiences and/or family history of SZ spectrum illness. The mean amplitude of early (80−220 ms) and mid-latency (160−290 ms) ERP components, registered over 5 midline electrodes (Fz, FCz, Cz, CPz, Pz) during a passive auditory oddball task, were used as machine learning features. RSz classification was performed using KNN, DT, and SVM classifiers. Both classifiers achievied accuracies of approximately 44 %, suggesting that the ERP features used were not sufficiently discriminative. The reduced accuracy may be accounted for by developmental factors. Maturational changes may lead to increased variability in the brain's response to stimuli in the environment, resulting in morphological alterations of the EEG signal and, consequently, rendering the direct comparison of ERP responses difficult [133].

6.1.3. *Distinguishing SZ from other psychiatric disorders*

EEG-based machine learning algorithms have also been used to distinguish SZ from other psychiatric disorders. Alimardani *et al.* [129] tested the discrimination of bipolar disorder and SZ patients, who share symptomatic features [134], using an EEG feature-based classifier

Fig. 2. Accuracies achieved with machine learning classifiers (identified in dot labels) using extracted features (x-axis) for SZ binary classification performed in different EEG datasets. Dot color represents the EEG paradigm used for data collection (auditory, visual, and working memory tasks, resting-state, and combined data from visual and resting-state paradigms), whereas dot size reflects the total number of subjects. It is worth noting that some results may overlap, which is reflected in the color combination of the corresponding conditions. **Abbreviations:** MNE – cortical density determined by minimum-norm estimate; SPN – spatial pattern network.

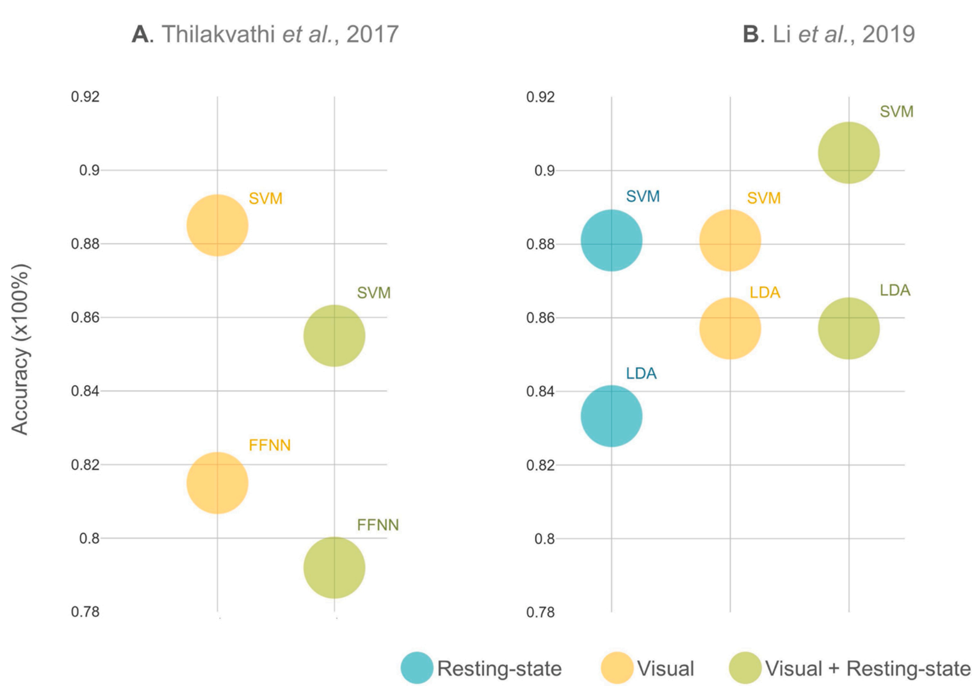

Fig. 3. Classification accuracies achieved by Thilakvathi *et al.* [117] and Li *et al.* [118] using features extracted from EEG signals collected during visual and resting state conditions. The representation of these results follows the same configuration as Fig. 2.

framework. Patients with SZ were identified with a 91.30 % maximum accuracy, when applying the kNN classifier on EEG signal-to-noise ratio (SNR) features [129]. Despite its relevance, the potential of machine learning methods to discriminate SZ from other psychiatric disorders using EEG data has received little attention.

6.2. Novel approaches: the prospects of deep learning

The accurate results obtained with classical machine learning methods corroborate the value of specific features of the EEG signal to detect and classify SZ. However, both feature extraction and selection require domain expertise, and specifying which are the most relevant has proven difficult. Deep learning, a machine learning branch, has greatly improved learning performance in computer vision and image recognition [135]. Deep learning has the capacity to extract meaningful patterns from available data, without human bias. Deep learning methods have surpassed machine learning based on feature engineering in most fields [136,137], and recently their potential in the realm of SZ diagnosis has also been explored.

6.2.1. Deep learning algorithms

Representation learning not only grasps the mapping of data representation onto the output but it also learns the representation itself [93]. Therefore, this machine learning subfield might lead to improved performance compared to classical algorithms [93].

Deep learning is highly relevant in pattern recognition in digital representations. Through neural networks, these algorithms attempt to reproduce the neocortex's layers of neurons and their activity [138]. This sophisticated technique can extract abstract, high-level features from raw data, allowing computers to build complex concepts from simpler representations [93]. Deep learning depth relies on a multilayer model architecture, which allows executing more instructions and increases the algorithm power [93]. Whereas in traditional approaches the representation and classification are separately optimized, the optimization of both phases in deep learning is performed through a backpropagation algorithm that determines how a machine should change its internal parameters [135]. Different variants of deep architectures have been developed [139]. Deep learning algorithms use ANNs, multiple-layer neural networks based on fully connected nodes (artificial neurons) [139]. Recent deep learning architectures have relied on three classes of ANNs: MLPs, CNNs, and RNNs. MLPs learn a representation from all data input, CNNs exploits the spatial structure of data by computing filter-selective feature maps, whereas RNNs process sequential data introducing the concept of memory [93,139].

EEG-based deep algorithms have seen a growing interest in brain-signal decoding [140–143]. Few studies attempted SZ classification using deep learning based on EEG signals. Table 4 lists the studies that explored the prospects of EEG-based deep learning. These studies mostly relied on resting-state data and achieved higher accuracy using CNNs.

CNN represents the most relevant component in the architecture of EEG classification solutions [144]. Biologically inspired in the organization of the primary visual cortex, the CNN represents a successful application of knowledge on brain function to machine learning implementations [145,146]. In a convolutional layer, the dot product between a restricted portion of the input and the kernel (set of learnable parameters) is computed [147]. Then, the kernel is convolved across all input width and height, producing a feature map. CNN features are defined as spatial 2D maps. The CNN layers are hierarchically arranged, allowing the detection of more complex patterns after the detection of simpler features [93,147].

6.2.2. Deep learning for SZ binary classification

Phang *et al.* [149] proposed a framework for SZ binary classification based on CNN. A combination of time-domain, frequency-domain, and topological measures of brain connectivity were used as model input, named multi-domain connectome (MDC). Each domain measure was fed into a 1D- (for the topology-based complex network) and 2D-CNN (for time and frequency domain measures) models. The MDC obtained accuracies above 90 %. The combination of measures improved classification performance when compared to single-domain features [149].

Table 4
SZ classification attempts using representation learning methods based on resting-state EEG signals. The selected studies were categorized according to type of classification.

Classification Task	Author [Reference]	Year	EEG Channels	Sample Size	EEG task	Input Data	Architecture	Classifier	Evaluation Method (Train/ Validation/ Test)	Test set Size	Accuracy*
SZ vs. HC	Oh [148]	2019	19	14 HC; 14 SZ	Resting-state	Time-domain representation	CNN	Softmax	10-fold cross-validation (72 % / 18 % /10 %)	14 HC; 14 SZ ⊗	81,26 %
	Phang [149]	2019	16	39 HC; 45 SZ	Resting-state	Fusion of time, frequency, and topological connectivity	RNN, CNN	Softmax	5-fold cross-validation (60 % / 20 % / 20 %)	39 HC; 45 SZ ∅	92.87 %
	Calhas [150]	2019	16	39 HC; 45 SZ	Resting-state	Time-frequency EEG representation	SNN	SVM; RF; XGBoost; NB; kNN	Leave-one-out cross-validation	39 HC; 45 SZ ∅	83 %
	Naira [151]	2019	16	39 HC; 45 SZ	Resting-state	Matrices of correlation between channels	CNN	Softmax	(70 % / 30 % / -)	4% of input segments ⊕	90 %
HC vs. 'at risk' vs. SZ	Chu [152]	2017	64	40 HC; 40 FE; 40 CHR	Resting-state	Time-domain and frequency-domain	ANN; CNN; RNN	Softmax; RF; SVM	Cross-validation (n.d.)	40 HC; 40 FE; 40 CHR ∅	92.5 % [a]
	Ahmedt-Aristizabal [128]	2020	30	40 HC; 65 RSZ	Passive auditory oddball	Spatio-temporal EEG representation (EEG time course across electrodes)	CNN + LSTM	Sigmoid Activation	5-fold cross-validation (64 % / 16 % / 20 %)	40 HC; 65 RSZ ⊗	72.54 %

*Concerning the method with the best performance (bold in the *Architecture* and *Classifier* column) [a]Three groups comparison.
⊗ subject-independent evaluation ⊕ subject-dependent evaluation ∅ subject dependency level not specified.

Calhas *et al.* [150] also tested a CNN-based model on resting-state EEG to identify discriminative features of SZ. The model's architecture relied on a SNN, composed of two "twin" convolutional sub-networks: each sub-network receives an input sample, which corresponds to a Discrete Short-time Fourier Transform representation of a one-minute long signal, extracted from one channel of each subject. Samples from different subjects were paired by channel. The output feature maps of each sub-network were compared, assessing samples' similarity. The network learned the desired behavior through the pairwise distance metric. Subjects' classification was performed using the resulting feature maps fed into SVM, RF, XGBoost, NB, and kNN classifiers. RF classifier achieved an accuracy of 84 % [150]. Naira and José [151] used the Pearson Correlation Coefficient to determine the relationship between 16 electrodes, hypothesizing differences in brain connectivity between SZ and controls. Images of the correlation matrices, created from 10-second resting-state EEG segments (six per subject), were used as input to the proposed 7-layer CNN-based model. SZ subjects were correctly recognized with an accuracy of 90 % [151]. Oh *et al.* [148] proposed an 11-layered CNN architecture for a subject-based classification of SZ. Resting-state EEG segments (25 s) from 19 electrodes were used as input data. The model was able to correctly discriminate SZ from HC subjects with an accuracy of 81.26 % [148].

6.2.3. Deep learning for at-risk state recognition

Chu *et al.* [152] proposed a subject-based recognition approach. Resting-state signals were recorded from HC, CHR, and FES participants. Besides testing ANN and RNN architectures, the best performance was achieved by combining a CNN model for feature extraction with an RF classifier. The highest accuracies were above 95 % for FES and HC groups, and approximately 80 % for CHR, using both time-domain and frequency-domain representations as inputs [152]. This is the only study exploring the potential of deep learning to differentiate prodromes from HC and FES. Accuracy was lower in at-risk subject identification than in HC or FES recognition. Notwithstanding, deep learning methods seem to improve the discrimination of the three groups relative to machine learning algorithms.

Evidence for improved performance of deep learning compared to classical machine learning methods was provided by Ahmedt-Aristizabal *et al.* [128] in the same study reviewed in section 6.1.2. These authors used event-related features from auditory processing components, which were insufficient to identify children at risk for SZ. Subsequently, they attempted classification using a deep learning model. In the new approach, they considered the EEG signal from the 300 ms post-stimulus temporal window, registered over the same 5 midline electrodes. Two-dimensional data structures were created (electrodes x timepoints) for each trial and used as input to the 2D-CNN-LSTM model, with one CNN and two stacked long short-term memory (LSTM) layers. The RSz trials were recognized with an accuracy of 72.54 % that clearly surpassed the 44.75 % accuracy obtained with a DT classifier [128]. However, this accuracy was nevertheless lower than the accuracy achieved by resting-state models. This may reflect developmental effects and, consequently, an increased variability of EEG signals, as previously discussed. The combination of convolutional and recurrent neural networks led to an accurate discrimination of EEG signals from children at-risk of SZ conversion. This suggests that abnormalities in auditory stimuli processing also occur in prodromal phases of SZ.

With the exception of the study of Ahmedt-Aristizabal *et al.* [128], deep learning methods for both SZ classification and at-risk discrimination have relied on resting-state EEG and on time and frequency-domain signals as input data. Despite the lack of studies focusing on event-related signals, the accuracies achieved show that CNN models can successfully identify discriminative features of SZ. Even though deep learning methods have not been applied to the classification of different phases of the SZ spectrum based on event-related signals, the results reported by Ahmedt-Aristizabal *et al.* [128] highlight the promise of these methods in predicting SZ.

7. Promises and pitfalls

The studies reviewed in the current paper reveal the potentialities of EEG-based machine learning algorithms in discriminating SZ from HC, at-risk, and bipolar disorder subjects (>71 % of accuracy). Some ERP measures, previously proposed as SZ biomarkers (e.g., P300, MMN, or N100), and the resting-state signal complexity were found to represent reliable features, though others have been equally successful such as statistical measures or oscillatory power. The SVM was the most commonly used classifier due to its computational efficiency [153], achieving the best performance in most studies.

The advantages associated with both the use of raw EEG data instead of EEG features defined *a priori* and with the capacity to learn subtle patterns from EEG data reinforce the potentialities of deep learning methods in tackling the challenge of identifying brain signatures of the SZ spectrum and illness course. Although few, the most recent studies reflect the growing interest in deep learning methods, which allow automatic feature extraction from resting-state EEG data and discriminate SZ from HC with accuracies above 83 % using CNNs. The successful discrimination between normal, at-risk, and/or subjects with clinical symptoms is crucial for SZ prediction and prognosis. Resting-state and auditory event-related EEG signals were used to probe the capacity of these methods to recognize at-risk subjects, achieving accuracies of 80 % and 72.5 %, respectively. The performance achieved by the deep learning architecture relying on event-related signals represented an improvement of almost 30 % in accuracy compared to common classifiers, such as DT or SVM, fed with amplitude measures of ERP components. Unlike the models applied to resting-state measures, Ahmedt-Aristizabal *et al.* [110] not only used CNN in their proposed architecture but combined convolutional with recurrent layers. Specifically, the use of CNN has allowed correlating temporal, frequency, and spatial information extracted from EEG data and has proven a successful strategy in classifying SZ. However, recurrent networks such as LSTM are designed to process temporal or sequential information. These networks can play an important role in the process of learning patterns from task-related EEG signals, which correspond to sequences of ERP components. These promising results encourage the applications of deep learning to EEG data, in particular to event-related signals, whose features may reflect cognitive, affective, or sensory changes in SZ.

Although risk prediction is important for early detection and treatment, the revised studies focused on diagnosis. This is indicated by the preference for supervised learning techniques rather than other machine learning methods. The supervised algorithms are designed based on labelled datasets. Data from SZ patients are typically obtained after diagnosis is confirmed based on standardized methods, such as DSM-5, which mostly relies on symptom evaluation and self-reports. The proposed machine learning methods should not be considered substitutes for the gold standard diagnosis instruments (DSM-5/ICD-10); instead, they align with the RDoC framework purposes. Specifically, EEG-based machine learning may improve the detection and establishment of relationships between neurobiological signals and clinical symptoms, providing insights into the pathophysiology of SZ. Nevertheless, other limitations should be noted. The complexity of deep learning architectures, in general, is reflected in a difficult interpretation of the models, being particularly challenging to identify the most influential features of the data [154]. Whereas in classical machine learning methods the relationship between the input variables and the models' output is understandable, the deep learning architectures, data sources, and training conditions hamper the comprehension of their internal representations. To overcome this limitation, interpretation techniques have been developed and implemented [155]. This could be an added value in understanding which information from the time course, frequency, or topographic distribution of the EEG signal contributes the most to the prediction. Together with clinical data (e.g., validated clinical scales and patients' self-reports), this information may reveal the functional significance of the EEG features that are altered in SZ.

Another limitation is the quantity and quality of brain data on which the performance of machine learning algorithms depends. Since the sample size is critical, it should be representative of the SZ population or other psychiatric disorders whose data will guide the algorithm learning process [156]. In the studies included in this review, the number of subjects tested was variable and generally small, which limits the generalization of the current findings. Based on a large number of features and small sample sizes, the algorithm predictions might be inaccurate and not generalize well, representing a case of overfitting. Thereby, a thorough validation is necessary to avoid amplification of data errors and biases. An appropriate methodological approach is the combined use of a validation dataset, allowing the fine-tuning of model hyperparameters, and an independent test set to evaluate the final model's performance and generalization error in an unbiased manner [92]. Non-overlapping subjects' data in training, validation, and test sets should be ensured [156]. Most of the described studies used leave-one-out or *k*-fold cross-validation (5- or 10-fold, predominantly) methods, which represent resampling techniques used to enhance the model's generalizability. The size of train and test datasets, as well as the number of folds in cross-validation, depend on the sample size, number of features, and algorithm used [157]. However, cross-validation methods can also overestimate predictive accuracy and mask the true model generalizability [158]. Future studies will benefit from larger sample sizes and datasets to improve generalizability. In particular, the increase of training data allows testing more complex models and reduces overfitting [135].

Even though the usefulness of EEG as a functional neuroimaging tool is unequivocal, some challenges should also be considered when using this technique. Despite its relatively high portability and flexibility, electrically shielded and acoustically isolated rooms are recommended for EEG data collection to reduce noise. A controlled experimental design is also required to minimize EEG artifacts. Variations in signal-to-noise ratio across trials and subjects, which may also arise from differences in EEG data acquisition conditions, may affect the quality of the signal that is used as input in machine learning algorithms [159]. Moreover, EEG differences are expected between different subjects and across different sessions given the non-linearity and non-stationarity of these signals [160,161]. Longitudinal EEG data could inform on the generalization of the models across sessions and improve the capacity of those models to learn intrinsic information [162,163]. Finally, a well-characterized public SZ EEG database is highly recommended for the direct comparison and objective evaluation of different algorithms' performances. Only then it will be possible to accurately measure the effectiveness of the developed models and assess the usefulness of machine learning both for research and clinical applications.

Some of the clinical symptoms may overlap across psychiatric disorders [164]. Indeed, comorbidity is the rule rather than the exception in psychiatric disorders, which has implications for patients' diagnosis and treatment [164,165]. Therefore, its effects should be considered in SZ research [166,167]. As a potential limitation, the current review did not consider comorbidity as an exclusion criterion in studies assessed for eligibility, which may limit the interpretation of results. Notwithstanding, most of the studies included in the present review did not report whether the samples have been controlled for possible comorbidities. Future studies should address these issues.

8. Conclusions

The high heterogeneity of SZ and symptom overlap with other psychiatric disorders have challenged neuroscientists and engineers to develop more effective diagnostic and predictive tools. This review provided a critical analysis of classical machine learning and deep learning methods to detect SZ based on EEG signals, published in the last five years. Specifically, we discussed the potentialities and limitations of the algorithms used and their parameterization, both in task-related and resting-state EEG signals. This critical review also highlighted good practices for the development and implementation of machine learning methodologies applied to EEG signals.

Machine learning methods are not expected to replace the current diagnostic systems for SZ and other psychiatric disorders. Instead, advanced learning-algorithms may complement and aid the discrimination of SZ and HC, improve the identification of SZ biomarkers, and establish relationships between EEG measures and symptoms. These techniques, especially deep learning algorithms, offer promise in enhancing our understanding of the neural mechanisms underlying SZ. Considering the reduction of (time-consuming) feature engineering and the possibility of maximizing the use of unstructured data, deep learning shows great promise in this field.

The predictive value of future models may be transferred to clinical practice, reflecting the fruitful dialogue between computational sciences, neuroscience, and psychiatry. The described approaches represent a promising starting point for the development of EEG-based discriminative models that might predict the onset of SZ, identify subjects at high-risk of converting to psychosis or differentiate SZ from other disorders, promoting more effective early interventions.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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