

Review

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Review

The Therapeutic Loop: Closed-Loop Epilepsy Systems Mirroring the Read-Write Architecture of Brain-Computer Interfaces

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Abstract

Drug-resistant epilepsy (DRE) remains a major therapeutic challenge, as a considerable proportion of epilepsy patients fail to achieve seizure control with conventional anti-seizure medications or surgical therapy. Closed-loop systems have emerged as a promising alternative, offering patient-specific, on-demand neuromodulation. Despite notable advances in the academic domain, clinical translation has stagnated, and surgical resection remains the intervention with the highest probability of achieving seizure freedom. In this review, we delineate the principal limitations currently constraining progress in epilepsy neuromodulation and conceptualise these systems as instantiations of the read-write architecture characteristic of brain-computer interfaces. The read component entails the continuous acquisition and analysis of neurophysiological signals to predict or detect imminent seizures. In contrast, the write component involves the delivery of targeted interventions to disrupt epileptiform dynamics and prevent clinical seizure manifestation. We outline the closed-loop processing pipeline, survey the current state of the art, and discuss key methodological and translational challenges, particularly in algorithm validation and long-term reliability. Finally, we address patients' and caregivers' perspectives on the acceptance and practical integration of such technologies. This work synthesises current advances in the field and delineates the path toward fully autonomous clinically effective closed-loop neuromodulation as a viable treatment paradigm for DRE, aiming to improve patients' quality of life.

Keywords: drug-resistant epilepsy; seizure prediction; seizure detection; closed-loop; brain-computer interface

1. Introduction

Epilepsy stands as a chronic, noncommunicable neurological disorder affecting approximately 50 million individuals globally, ranking among the most common neurological conditions [1]. It is fundamentally characterised by the recurrent seizures, arising from sudden, excessive electrical discharges within neuronal clusters in the brain. While a single seizure does not constitute epilepsy, a formal diagnosis is established upon experiencing two or more unprovoked seizures [2].

Drug-resistant epilepsy (DRE) is a major clinical challenge [2,3], defined by the ILAE as the failure to achieve sustained seizure freedom after adequate trials of two or more appropriately chosen and tolerated anti-seizure medications (ASMs) [2]. While many patients respond to ASMs, 30–40% develop DRE [4,5], representing a high-risk population [6–8]. Risk varies with age and epilepsy type: early-onset epilepsy strongly associates with DRE [9–11], whereas adult-onset cases linked to progressive disorders or cortical lesions are also prone to pharmacoresistance [12–18], with focal epilepsies carrying particularly high risk [19–22].

DRE imposes significant economic and societal burdens [22–25], exacerbated by psychiatric comorbidities [26,27] and social marginalisation [28,29]. Families and caregivers experience emotional, financial, and social strain [30–34], and care demands are higher than for pharmacoresponsive patients [35–37]. In high-income countries, direct healthcare costs may be 2–10 times higher, up to €9,000 per patient per year [37–39], while limited treatment access in low- and middle-income countries worsens socioeconomic impact [40,41].

Resective surgery of the epileptogenic zone remains the most established alternative after ASM failure [42,43], with durable seizure freedom achieved in 50% of focal neocortical and two-thirds of temporal lobe epilepsy patients when the epileptogenic network is accurately identified [44–51].

For patients unsuitable for resection, neuromodulation systems offer complementary strategies [52,53], delivering interventions that prevent generation or disrupt ongoing seizures [54,55].

As of today, only a limited number of neuromodulatory therapies are commercially available and approved in both the European Union and the United States (see Table 1). These include the Responsive Neurostimulation System (RNS) [56], Vagus Nerve Stimulation (VNS) [57,58], Deep Brain Stimulation of the Anterior Thalamus (DBS) [59,60], and External Trigeminal Nerve Stimulation (eTNS). Among them, DBS, eTNS, and the first-generation VNS operate under an *Open-Loop System* (OLS) architecture (Figure 1A), wherein stimulation parameters are predefined and delivered independently of ongoing neural activity. In contrast, RNS and the latest VNS iterations [61,62] implement a *Closed-Loop System* (CLS) architecture (Figure 1B), integrating continuous monitoring of brain—or surrogate—signals to predict or detect seizures and deliver temporally precise interventions [63–65].

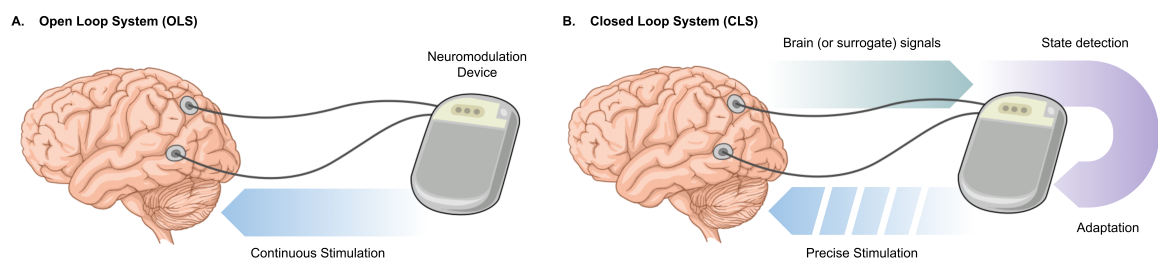


Figure 1. Overview of neurostimulation architectures. **(A)** *Open-Loop System* (OLS). Stimulation is administered using predefined settings that operate independently of the patient’s real-time neural state. **(B)** *Closed-Loop System* (CLS). The device acquires neural signals (or surrogates thereof), detects candidate windows for intervention, and dynamically modulates its stimulation parameters to deliver precise, adaptive neuromodulation.

Recent developments have introduced the concept of Adaptive Deep Brain Stimulation (aDBS) [66,67], an evolution of conventional DBS that integrates feedback-driven modulation. Notably, Medtronic’s Percept™ PC, although currently operating as an open-loop device, has the technical capability to operate in a closed-loop framework. Other experimental approaches, such as Repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS) [68], were initially conceived as OLS modalities but are increasingly being adapted to CLS frameworks [69–71]. Collectively, these trends reflect a decisive shift in neuromodulation research towards CLS paradigms, aiming to achieve patient-specific, autonomous, and dynamically responsive therapy. Such systems hold the promise of enhancing efficacy, minimising adverse effects, and optimising long-term therapeutic outcomes.

With respect to their mechanism of action, current evidence supports two forms of stimulus-driven modulation. The first is direct suppression of electrographic seizure patterns (ESPs), wherein triggered electrical stimulation inhibits an ongoing seizure, consistent with the classical understanding of RNS. The second is direct frequency modulation, a recently described phenomenon in which stimulation reshapes the spectral content of ESPs [72]. Notably, in both modalities, the therapeutic benefits of CLS seem to emerge through progressive adaptations within the seizure network, rather than through the immediate termination of individual ictal events, suggesting a potential disease-modifying mechanism [55]. Then, crucially, the therapeutic efficacy of CLS-based neuromodulation

depends on constant accurate state detection or prediction, enabling the precise delineation of the temporal window during which patient-specific interventions can effectively be administered. From a technical standpoint, CLS architectures intended for clinical deployment represent a specialised subclass of Brain–Computer Interfaces (BCIs), as they continuously acquire neural signals and translate them into adaptive therapeutic outputs without requiring human supervision or explicit user control.

Table 1. Contemporary neuromodulation systems used for drug-resistant epilepsy.

System	Architecture	Approval Status	Examples
VNS (conventional)	OLS	Adjunctive therapy (CE 1994 (EU); FDA 1997 (US)) [73]	NeuroCybernetic Prosthesis System
VNS (latest)	CLS	Adjunctive therapy (CE 2014 (EU); FDA 2015 (US))	AspireSR® and SenTiva®
DBS	OLS with CLS capability	Adjunctive therapy (CE 2010 (EU); FDA 2018 (US)) [55,74]	Percept™ PC
RNS	CLS	Adjunctive therapy (FDA 2013 (US) [75])	NeuroPace RNS® System
eTNS	OLS	Adjunctive therapy (CE 2012 (EU))	Monarch™ eTNS™
rTMS	OLS and CLS	Investigational	
tDC	OLS and CLS	Investigational	

However, the efficacy of available neuromodulation BCIs in epilepsy remains fundamentally palliative rather than curative [76–79]. For instance, while RNS achieves significant seizure frequency reductions (50–70%), durable seizure freedom rates remain low (8.7–21.1%) [80–83]. Similar outcomes are reported for VNS (6.9–11%) [84–86] and DBS (1.32–8.9%) [82,83,87–89]. It should also be noted that the definition of seizure freedom varies between studies, with many adopting the criterion of no seizures for at least one year. While clinically meaningful, such an interval does not constitute true long-term seizure freedom if relapse subsequently occurs. Nevertheless, these findings underscore that surgical resection of the epileptogenic tissue offers a markedly superior, potentially curative outcome, with long-term seizure-freedom rates of approximately 50–66%, as previously noted.

Therefore, the core research problem, and the underlying motivation for this review, is to examine why seizure detection and prediction systems, despite their sophistication and their classification as a type of BCI reacting to precise patterns of brain activity, have failed to reach the durable curative efficacy benchmark often achieved by successful surgical resection. This stagnation indicates that significant fundamental challenges persist within the translational pathway from research to clinical deployment. This review will explore persistent bottlenecks, including data limitations and methodological shortcomings in performance evaluation.

2. The Plateau of Clinically Deployable Devices

To date, the RNS and modern applications of VNS (i.e., *AspireSR*®) remain the only commercially available CLS devices for epilepsy to have received approval from the US FDA and to be CE-marked in the European Union. Since their approval in 2013 and 2014, respectively, they have stood as the sole clinically established therapies routinely implemented for seizure modulation and prevention in patients with DRE. Although several other CLS systems have advanced to clinical or investigational trials in the intervening years, none has yet achieved regulatory approval.

Given the considerable time elapsed since the introduction of RNS and VNS, it becomes evident that progress in neuromodulation through seizure detection and prediction has advanced more slowly than initially anticipated, especially considering that state-of-the-art algorithms now surpass these systems in performance. *Sisterson et al.* [90] reported that RNS achieved a mean accuracy of 90.0%

(interquartile range 84.3–98.8%, range 63.0–100%), sensitivity of 51.5% (interquartile range 48.7–50.1%, range 0–100%), and specificity of 93.2% (interquartile range 90.6–99.6%, range 64.5–100%). However, they observed substantial inter-patient variability in detector accuracy and noted that results were highly dependent on manually pre-defined thresholds. The authors also cautioned that the device's limited onboard storage allows only a small fraction of recordings to be retained, such that the derived performance summaries may misrepresent true sensitivity and specificity. Regarding CLS-VNS, *Boon et al.* [91] reported that multiple detector configurations achieved sensitivities $\geq 80\%$, but only for seizures accompanied by heart-rate increases, and that false positive rates ranged from approximately 0.5 to 7.2 events per hour, depending on the tachycardia threshold employed. Similarly, *Fisher et al.* [92] found that merely 34.8% of recorded seizures were actually treated by the VNS device. Despite these limitations, recent reviews of seizure detection and prediction algorithms demonstrate that numerous contemporary approaches perform on par with, or even exceed, the capabilities of RNS and VNS [54,93–95]. Nevertheless, these advances have yet to translate into clinical adoption. This stagnation suggests that fundamental scientific and translational challenges remain unresolved, and that key bottlenecks persist along the pathway from research to clinical application.

Rather than directly addressing the core challenges, the seizure detection and prediction community progressively shifted its emphasis from real-time brain state identification towards more probabilistic or circadian-based *forecasting* of seizures [96]. In this paradigm, the objective is no longer to classify discrete brain states but instead to estimate the likelihood of a seizure occurring within a given time window. While such forecasts can offer valuable clinical benefits, enabling patients to take safety precautions or find a secure location, they are fundamentally incompatible with a proper BCI architecture. The inherent imprecision of these forecasts makes them unsuitable for defining the sharp limits required to close the therapeutic loop in BCIs, whose core purpose is to provide autonomous and automated therapeutic intervention.

A prominent example of this forecasting approach was the *NeuroVista Seizure Advisory System*, an implantable device that forecasted seizures based on continuous intracranial EEG (iEEG) recordings [97]. The system transmitted neural data wirelessly from cortical electrodes to an external receiver that generated warnings of impending seizures. In the pivotal Melbourne trial, the device achieved predictive performance above chance in a subset of patients, yielding clinically useful forecasts in approximately half of the cohort. However, for several participants, the system proved ineffective, either failing to generate timely warnings or producing excessive false alarms. These mixed outcomes, combined with practical limitations such as device maintenance requirements and dependence on a handheld receiver, ultimately led to the termination of both the trial and the sponsoring company.

Following the trial's discontinuation, the collected data were released as part of the Melbourne University AES/MathWorks/NIH Seizure Prediction Challenge on Kaggle. Many community-developed algorithms improved average sensitivity 1.9 times with respect to the original NeuroVista model, particularly in the most challenging patient cases [98]. Building on this achievement, the organisers established the platform *Epilepsyecosystem.org*, which serves as a collaborative hub for data and algorithm sharing, fostering a crowdsourced approach to advancing seizure prediction research.

Despite these advances, it is noteworthy that the enhanced algorithmic performance did not translate into renewed clinical development of the NeuroVista system. This outcome suggests that, even with substantial methodological progress, the forecasting paradigm alone may be insufficient to address the broader challenge of effective closed-loop seizure control. A likely explanation is that probabilistic forecasting, by definition, cannot specify the precise real-time intervention windows required for a genuine CLS. The effectiveness of such systems hinges on accurately identifying the temporal intervals during which stimulation must be delivered to prevent or interrupt seizure onset. While forecasting may hold potential for patient warning systems or wearable alert devices, this inherent functional limitation may preclude its application as a true epilepsy BCI.

3. Scarcity of Complete Public Datasets

The fundamental prerequisite for the successful development of BCIs is the availability of high-quality, large-scale datasets. It is well established that large datasets are advantageous for training deep learning models as they provide the statistical power required to capture the variability of brain signals both within and across subjects, contexts, and recording environments [99,100]. Such variability is essential to design BCIs that function reliably outside controlled laboratory conditions.

However, dataset quality and relevance are equally important. For instance, early-stage development of novel signal processing methods can often be undertaken successfully using smaller, more focused datasets [101]. Several studies have demonstrated that even relatively small EEG/ECOG datasets can train effective BCI decoders, especially when the recorded features are well-defined and consistent across sessions or subjects [102–104]. Nevertheless, when developing robust real-world systems capable of adapting to diverse users and environments, the availability of larger and more heterogeneous datasets becomes critical [105].

Beyond the sheer volume and fidelity of recordings, contemporary BCI development emphasises the adoption of standardised data formats, such as the Brain Imaging Data Structure (BIDS) and its extensions for EEG and MEG, as well as adherence to open data principles [106,107]. Implementing community standards such as BIDS, in combination with containerised *BIDS-Apps* and standardised preprocessing pipelines, enhances data interoperability, reproducibility, and the portability of analysis workflows across research sites [108,109].

In contrast to these general trends in BCI research, one of the principal obstacles to epilepsy-oriented BCIs is the scarcity of publicly accessible datasets for seizure detection and prediction [110,111]. The existing datasets often lack a consistent format, needing time-consuming harmonisation efforts before any comparative analysis. In some cases, harmonisation is impossible due to incompatible acquisition protocols or incomplete metadata.

The aforementioned NeuroVista clinical trial represents a pivotal, albeit underexploited, milestone. It demonstrated that open data and crowdsourcing can serve as powerful catalysts for biomedical innovation, even in a condition as complex and heterogeneous as epilepsy. Despite this compelling proof of concept, epilepsy research has not fully embraced open-data practices comparable to those driving progress in motor and language BCIs.

3.1. Current Available Datasets

To systematically assess the availability of electrophysiological datasets for epilepsy research, a literature review was conducted using PubMed, IEEE Xplore, and Google Scholar. The search strategy employed the terms [(epilepsy[Title/Abstract]) AND (dataset[Title/Abstract])]. Peer-reviewed publications, institutional repositories, data-sharing platforms (e.g., PhysioNet, Kaggle, EBRAINS), and personal communication with dataset authors were examined to identify relevant resources.

Datasets were included if they met the following criteria: (i) they contained patient-level electrophysiological recordings of seizures; and (ii) they were publicly accessible, either directly or free of charge upon request.

For each identified dataset, the following characteristics were extracted: (1) cohort size (N); (2) age group of participants, categorised as adult or paediatric; (3) recording duration per patient (L); (4) inclusion of DRE patients; (5) availability of information on the resected brain area in cases where surgery had been performed; (6) presence of longitudinal follow-up data when applicable; (7) the neuroimaging or electrophysiological modality used for data acquisition; and (8) the information disclosed in the metadata, if available.

A total of 11 datasets were identified. A summary of the reviewed datasets and their characteristics is presented in Table 2.

Table 2. Current publicly available datasets containing human epilepsy data.

Dataset	N	Age	L	DRE	Resect.	Img. Tech.
NeuroVista Trial Data [97]	15	Both	Long-term	Yes	No	iEEG
HUP iEEG [112]	58 ¹	Adult	25 min	Yes	Yes	ECoG or SEEG
Epileptic EEG Dataset [113]	6	Unk.	2h	No	No	EEG
TUH EEG Epilepsy Corpus [114]	100	Unk.	Long-term	No	No	EEG
CHB-MIT Scalp EEG Database [115]	22	Both	9-42 h	Yes	No	EEG
Siena Scalp EEG [116]	14	Adult	3.3-24 h	No	No	EEG
Xiaoya Fan et al. 2019 [117]	23	Unk.	6-38 h	Yes	No	SEEG
SeizeIT2 [118]	125	Both	Long-term	Yes	No	Var. ²
Mesoscale Insights [119]	5	Adult	Unk. ³	Yes	Yes	ECoG & SEEG
Petr Nejedly et al. [120]	39	Adult	5.07 h	Yes	No	SEEG
Fragility Multi-Center [121]	91	Adult	1 min ⁴	Yes	Yes	ECoG or SEEG

¹ SEEG was recorded for 38 patients; ² Behind-the-ear EEG, ECG, EMG, and movement (accelerometer and gyroscope); ³ 10 mins before seizure, seizure (undefined length), and 5 mins post seizure; ⁴ 30 seconds before and after the ictal event.

Among the available datasets, cohort sizes are generally adequate for academic research (mean = 45.27, SD = 42.11, median = 23), yet remain insufficient for clinical trials. The required sample size in such trials depends on factors including the primary endpoints, expected effect size, and statistical power, which vary considerably across studies. Nevertheless, pivotal (registration) trials typically enroll around 200 participants [122,123]. This requirement may be even higher for Class-III (high-risk) implantable devices, where both safety and efficacy must be demonstrated across heterogeneous populations.

Regarding age groups, five datasets included only adult participants, three included both adult and paediatric patients, and three did not disclose participant's ages. This distinction is relevant, as age strongly influences both epilepsy prevalence and the probability of developing drug resistance.

Recording duration per patient (*L*) was highly heterogeneous, ranging from 1 minute to 183.8 days. Notably, six of the eleven datasets provided continuous long-term recordings, whereas the remaining five contained preselected clips.

Most datasets (8/11) focused exclusively on patients with DRE. Only three datasets reported information on resected brain regions following presurgical evaluation. Of these, just two included follow-up data to verify whether surgery was successful, thereby confirming whether the epileptogenic network had been resected or at least impaired.

Regarding recording modalities, four datasets were acquired using scalp EEG, two using SEEG, two using SEEG or ECoG, one combining SEEG and ECoG, one using iEEG, and one employing a multimodal wearable system including behind-the-ear EEG, ECG, EMG, and movement sensors (accelerometer and gyroscope).

The availability of patient-level metadata also varied considerably. Four datasets provided complete anonymised clinical and demographic information; three included no metadata at all; one contained age, sex, and seizure classification; one provided age and sex; one reported only sex; and one included only the putative seizure onset zone (SOZ) as defined by clinical staff.

3.2. Why Is It So Difficult to Find Data?

Strictly speaking, the challenge does not lie in the *existence* of data but in its *availability for sharing*. Hospitals with epilepsy monitoring units routinely collect highly valuable long-term recordings of their patients, together with the associated clinical metadata required for research. There is evidence that data are collected and stored but under-utilized due to ethical/regulatory constraints, despite the willingness of many centres and patients to collaborate with researchers [124–126].

The principal barrier in many jurisdictions arises from ethical and regulatory constraints. In the European Union, patient information cannot be shared without explicit consent, which must often be obtained anew for each study [127]. Moreover, regulations differ substantially across jurisdictions:

data that may be shared or accessed in one country may be subject to strict limitations in another [128]. This represents a significant setback, as vast quantities of clinically rich data remain effectively inaccessible [129]. Nonetheless, these regulatory frameworks play a crucial role in safeguarding patient information and ensuring anonymity [130].

4. Intrinsic Limitations

Having examined the limitations of publicly available datasets, several fundamental questions arise about how these datasets are defined and the assumptions that guide their use. The first pertains to how we conceptualise and delineate brain states, while the second concerns the expectations we hold regarding the dynamical activity of the epileptic brain.

4.1. State Definition

Although the existence of four principal brain states in epilepsy (interictal, preictal, ictal, and postictal) is widely recognised, precise definitions lack. This ambiguity represents a significant limitation for epilepsy-oriented BCIs, as accurate labelling of signal features is critical for successful system development. For instance, in language BCIs, the neural states to be identified are temporally well delineated, typically corresponding to spoken words or their cognitive representations. Similarly, in motor BCIs, the relevant states are clearly defined in time, reflecting the intention to execute a movement. These fields benefit from the ability to interact directly with participants, enabling the precise annotation of event onsets and offsets. Moreover, an extensive body of literature provides empirical evidence concerning the spatiotemporal organisation of language and motor functions in the brain. In contrast, temporal boundaries of epileptogenic brain activity remain imprecise, with multiple theoretical frameworks proposed and no definitive consensus achieved to date.

- The ictal state is the least controversial and the most clearly delineated [131,132]. Clinical experts have established behavioural and pathophysiological criteria that mark the onset and termination of seizures [133]. Minor discrepancies among clinicians are generally acceptable, and the community relies on these timepoint annotations as the *de facto* ground truth [134,135].
- In contrast, the preictal and postictal states are ambiguous [96,136]. For the preictal state, there is no agreement regarding its temporal onset. Proposed definitions range from minutes to hours, days, or even months before seizure onset [137–142]. Its underlying dynamics also remain unclear, both in terms of whether preictal states share common features across individuals with DRE, and whether a single patient experiences seizures preceded by distinct preictal patterns [142–144]. Pre-ictal definition relies on the seizure onset, however, it is possible that some preictal states never reach seizure transition due to regulatory brain activity. In these cases, an algorithm might correctly detect the pre-ictal state, but due to the lack of ground truth it would be regarded as a false positive.
- Finally, the interictal state is often defined simply as all remaining periods outside the preictal, ictal, or postictal windows. It is inherently dependent on the delineation of seizure-related states, and consequently liable to error.

4.2. Long-Term Changes in Brain Dynamics

Most existing methods for brain-state classification in DRE assume that brain dynamics remain relatively stable over time. Within this framework, training an algorithm on previously acquired samples is expected to ensure reliable classification of future instances. In practice, this entails developing models on a bounded portion of patient data, with the expectation that their performance will generalise across subsequent periods.

This assumption, however, is at odds with biological reality. Brain dynamics are inherently non-stationary and evolve over time, both in epilepsy and in healthy function. It is well established that neural activity patterns exhibit gradual changes, a phenomenon known as *drift* [145]. Drift can

degrade decoding performance, so BCIs in other domains employ adaptive algorithms to dynamically adjust to changes in neural signals in real time, by continuously updating decoding parameters.

In epilepsy, evidence for non-stationarity is even more compelling. Seizures induce recurrent reorganisation of brain networks, progressively worsening the disorder when left untreated [146–148]. Pre-ictal variability in functional connectivity distinguishes seizure types in mesial temporal lobe epilepsy (TLE) [149], and TLE patients exhibit accelerated dynamics and increased temporal instability relative to healthy controls with DRE showing greater temporal variability [150]. This indicates that seizure generation dynamics are drifting rather than remaining stationary. Furthermore, models that adapt to concept drift in EEG over long recordings significantly outperformed static models [151]. Nevertheless, most existing algorithms are designed under the assumption of data stability and consequently underperform when confronted with the evolving nature of real-world data.

5. The Depth-Breadth Dilemma

Broadly speaking, research in seizure detection and prediction has followed two dominant methodological paradigms: (1) *patient-independent (or general)* algorithms, designed to operate across diverse patient populations, and (2) *patient-specific* algorithms, tailored to the neurophysiological patterns of individual patients [152–154]. Both approaches have merits and limitations, and both continue to be actively explored in the field.

5.1. Breadth: General Paradigm

The breadth-oriented strategy aims to develop a “one-size-fits-all” solution by training models on large, heterogeneous datasets comprising recordings from multiple patients. The goal is to identify generalisable neural features that can signal or predict seizures across individuals. These models are often based on deep learning, designed to operate in previously unseen patients with minimal or no retraining [155,156].

The principal advantage of this approach lies in its scalability. A single validated model could, in principle, be deployed across diverse clinical settings without the need for extensive patient-specific optimisation. Moreover, such models require substantially less data per patient, particularly valuable in cases of infrequent seizures [156,157].

However, epilepsy is profoundly heterogeneous in seizure morphology, onset dynamics, and background activity. General models struggle to capture these patient-specific features, resulting in reduced sensitivity and specificity [158–160]. The high degree of inter-patient variability remains a fundamental limitation of the general-oriented paradigm.

5.2. Depth: Patient-Specific Paradigm

In contrast, depth-oriented approaches focus on training algorithms uniquely for each patient. These models learn the individual’s specific electrophysiological “fingerprint” during interictal, preictal, and ictal states, and frequently achieve superior performance in accuracy, sensitivity, and reliability [161,162].

Nevertheless, training such models requires substantial patient-specific data, typically multiple recorded seizures and long interictal/preictal recordings to capture the relevant features and account for variability over time [163]. This limits clinical applicability, especially for patients with infrequent seizures. Moreover, patient-specific models lack generalisability, as a model trained on Patient A generally does not perform well for Patient B.

It is important to emphasise, however, that most current BCI systems prioritise subject-specific strategies rather than adopting a general approach due to inter-individual variability in electrophysiological patterns. Decoding accuracy and system responsiveness are strongly influenced by user-dependent neural characteristics [164–166]. Workflows rely on tailoring feature extraction, frequency band selection, and adaptive protocols to the individual [166,167]. Such personalised designs have been consistently shown to improve performance, speed, and reliability across both medical and non-medical BCI applications [168,169].

5.3. Prevailing Trends and Emerging Solutions

Although both paradigms remain under investigation, the field tends to converge on the view that patient-specific algorithms consistently outperform general models.

A hybrid strategy has recently gained traction in the form of *transfer learning*, which aims to reconcile the advantages of both approaches [163,170,171]. In this paradigm, models are first pre-trained on large, heterogeneous datasets and subsequently fine-tuned using small amounts of patient-specific data. Transfer learning thus offers a pragmatic compromise, enhancing scalability while retaining a degree of personalisation necessary for clinically reliable seizure prediction and detection. Nevertheless, direct subject-specific modelling continues to outperform hybrid methods in many practical scenarios where individual variability exerts a dominant influence on system performance.

6. Methodological Issues in Performance Evaluation

A persistent challenge in the field is the absence of a standardised system for assessing and benchmarking detection and prediction algorithms [172].

The choice of validation strategy determines the performance estimates, as even subtle variations in data segmentation or metric computation can yield markedly different outcomes for the same algorithm [173–175]. Most top-performing approaches employ cross-validation (CV) schemes commonly used in machine learning (Figure 2A), in which data are typically divided into an 80/20 train–test split, sometimes combined with k -fold or leave-one-(seizure)-out cross-validation (LOOCV). *Shafieezadeh et al.* [175] demonstrated the limitations of this framework, showing that random 5-fold CV can inflate performance, improving accuracy by nearly 30% compared with LOOCV. Similarly, *Pale et al.* [173] reported that algorithms achieved up to a 7% higher F1 score under LOOCV than under time-series cross-validation (Figure 2B), an evaluation strategy that preserves the chronological structure of the data by ensuring that training always precedes testing in time. Both studies highlight that training on excessive or distant data can lead to overestimation of performance and should be avoided. In practice, once deployed, algorithms must contend with patient-specific variability and unseen dynamics not represented in the training set. This methodological disconnect likely contributes to the persistent gap between algorithmic advances and their clinical translation [176].

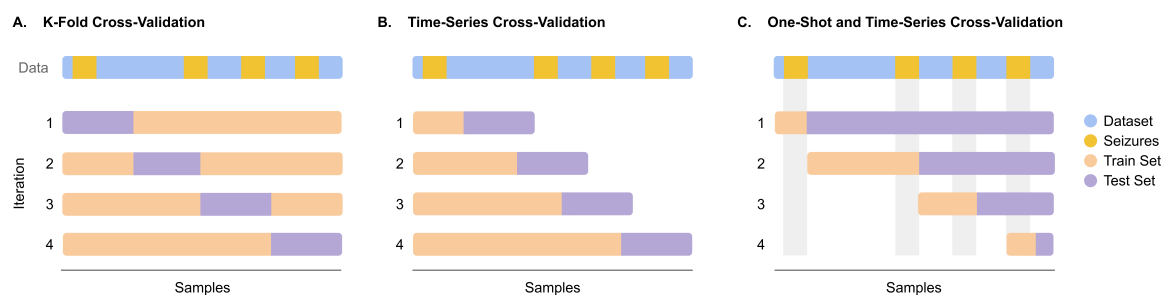


Figure 2. Schematic representation of performance evaluation techniques. **(A)** *K-fold Cross-Validation*. The dataset is partitioned into folds used iteratively for training (orange) and testing (purple). Conventionally, the training set is larger than the test set, and in several folds the training data are chronologically older than the test data (e.g., iterations 1–3). **(B)** *Time-series Cross-Validation*. Training sets always precede their corresponding test sets in time, preserving the temporal structure of the data; the training set remains larger than the test set. **(C)** *One-Shot Time-Series Cross-Validation*. The training set is restricted to a single (or a small number of) chronologically earlier instances, which always precede the test set, providing a stringent temporally faithful evaluation.

Although no gold-standard benchmarking system currently exists, some efforts are underway. In seizure detection, one notable initiative is *SzCORE* (Seizure Community Open-Source Research Evaluation framework for the validation of EEG-based automated seizure detection algorithms) proposed by Jonathan Dan and colleagues [177]. By contrast, in seizure prediction, the definition of a standard validation framework is stagnated by the lack of consensus on preictal state definition [178].

But even in frameworks such as SzCORE, several parameters remain at the discretion of research teams. These include, for example, the permitted overlap between ground-truth and predicted events, the tolerance for onset/offset alignment, and constraints on event duration. While such flexibility permits diverse applications of seizure detection algorithms, it simultaneously undermines comparability across studies. At present, the field lacks a universal method for empirically measuring and directly comparing algorithm quality.

7. Discussion

In this review, we have identified and critically examined the key factors that have hindered the advancement of epilepsy-related BCIs. Building on this analysis, the following discussion presents concrete strategies to overcome these obstacles and accelerate the translation of research outcomes into clinical practice. We also delineate those limitations that, in our assessment, are likely to persist despite current technological and methodological capabilities. We propose reforms in data acquisition and processing, a conceptual reframing of epileptic brain dynamics, and the redesign of epilepsy-oriented BCI systems and evaluation protocols to foster genuine clinical impact.

7.1. Dataset Improvement

7.1.1. Increasing Cohort Sizes

Given the high global prevalence of epilepsy, we argue that existing datasets should be substantially expanded. Enlarging cohort sizes would enhance diversity and statistical representativeness, thereby facilitating the development of models and enabling a more rigorous study of inter-individual variability.

The acquisition of electrophysiological data from patients with DRE, however, is time-consuming and constrained by clinical circumstances, as recordings can only be obtained from hospitalised patients undergoing evaluation. One potential strategy to mitigate the limitation of small cohort sizes is to aggregate data from multiple sources. Yet, as discussed in previous sections, public datasets remain markedly heterogeneous, often to the extent that merging two datasets becomes infeasible, even when similar recording modalities are employed.

Although many hospitals express willingness to share anonymised patient data, stringent regulatory frameworks prohibit the transfer of datasets beyond their hosting institutions without explicit participant consent, particularly within the European Union. These constraints are expected to become even more restrictive in the future. In such contexts, federated learning may offer a promising alternative by enabling collaborative model training without exchanging raw data. Nevertheless, this approach demands rigorous compliance with cybersecurity and data governance standards to ensure its safe and lawful implementation.

In any case, both data aggregation and federated learning depend on the adoption of harmonised standards. Existing and newly generated datasets should conform to interoperable structures that facilitate seamless integration. A set of proposed requirements to support such harmonisation is presented in the following sections.

7.1.2. Mimicking Real-Life Data

Datasets employed in academic research cannot realistically match the scale of those used in clinical trials or real-world practice, as doing so would substantially increase both the time and financial costs of research. Nonetheless, for neuromodulation systems to be effective, they must be trained on data that approximate real-world conditions [179].

The duration of recordings must be sufficient to capture the dynamic nature of brain states. Approximately half of the datasets presented in this review consist of only short segments surrounding seizures. Such restricted windows fail to reflect the broader temporal variability of brain activity, particularly interictal fluctuations. Ideally, datasets should encompass the whole clinical monitoring period, with a minimum duration of 24 hours. Longer recordings are especially valuable, as they

permit the study of multiday rhythms and infrequent events that may play a crucial role in seizure generation.

Where continuous long-term acquisition is impractical, it is important to recognise that seizures are relatively rare in real-world settings. Consequently, datasets should reflect this natural imbalance rather than artificially balancing interictal, preictal, and ictal samples. Preserving the natural overrepresentation of interictal periods enables models to extract more meaningful discriminative features of the preictal and ictal states, while also mirroring the event distribution observed in clinical practice.

A complementary strategy to address data scarcity is the use of data augmentation techniques, generating modified variants of existing recordings to artificially diversify datasets. Well established in other BCI domains, such approaches enhance generalisability, improve performance, and reduce overfitting. In the context of EEG, commonly applied augmentation strategies include temporal manipulations (e.g., time-warping, random cropping, or jittering), frequency-domain transformations (e.g., spectral scaling or filtering), and noise-based methods (e.g., Gaussian noise injection or channel dropout). More advanced approaches employ generative models such as variational autoencoders or generative adversarial networks (GANs) to synthesise physiologically plausible signals, increasing dataset diversity.

7.1.3. DRE Focus

Seizure freedom efforts are most clinically relevant when targeted at patients with DRE, for whom current treatments have failed. The mechanisms of seizure generation in DRE are likely to differ from those of drug-responsive patients, thus requiring dedicated investigation.

7.1.4. Metadata

Demographic and clinical metadata are frequently absent or incomplete in publicly accessible datasets, yet are essential for contextualising the electrophysiological recordings and stratifying modelling approaches. For instance, several paediatric epileptic syndromes remit spontaneously with age, so aggregating paediatric and adult recordings introduces confounding variability, biases statistical inference, and may obscure clinically meaningful network patterns.

We therefore advocate for the mandatory inclusion of, at minimum, the following metadata attributes: patient age, sex, ethnicity, epilepsy syndrome, preoperative Engel classification, indication of whether resective surgery was performed, and postoperative Engel outcome at ≥ 3 -year follow-up, as multiple studies show that seizure recurrence after epilepsy surgery is concentrated in the first 2-3 years, and that the probability of relapse declines and becomes more stable beyond that period (i.e., after 3-5 years post-surgery) [180–185].

In addition, comprehensive access to the structured content of patients' clinical records would be highly desirable to mitigate unobserved confounders (smoking habits, alcohol consumption, prior brain lesions, comorbid neurological and psychiatric conditions) that may influence neurophysiological dynamics [186–188]. Although there are practical barriers due to the unstructured, free-text nature of clinical documentation, large language models (LLMs) offer a promising avenue for automated information extraction. These systems could convert narrative reports into standardised metadata suitable for research workflows. However, such an approach must strictly comply with data protection frameworks (e.g., GDPR, HIPAA) and undergo rigorous validation to ensure both semantic accuracy and reliability before deployment in clinical or research contexts.

7.1.5. The Surgical Resection as an Additional Ground Truth

Epilepsy surgery to remove the pathological tissue is the most common treatment for DRE. Although knowledge of the removed area and postsurgical outcomes is not required for BCI development, it provides a clinical "ground truth" for localising the seizure onset zone and allows researchers to investigate network dynamics within and around the epileptogenic region. Postoperative follow-up at 3 to 5 years indicates whether or not the surgical resection captured the SOZ, as mentioned in the previous section. This is particularly relevant when invasive imaging techniques are employed,

targeting a brain area preselected by clinical staff, as clinicians may fail to identify the true SOZ in approximately 50% of cases. Post-resection follow-up, therefore, provides researchers with crucial information on whether the SOZ was indeed captured in the available recordings. Moreover, such data enable a more rigorous sub-selection of relevant signals, for example by restricting analyses to electrodes located within the SOZ.

7.2. Overcoming Intrinsic Limitations

7.2.1. Goal-Oriented State Definition

Given that the definition of the preictal state remains unresolved, two possible strategies can be considered. The first, and most systematic, is to prioritise research aimed at delineating the temporal and physiological boundaries of DRE brain states. Pursuing this path may delay the development of epilepsy BCIs.

Alternatively, BCIs could be developed concurrently by defining brain states in terms of the intended therapeutic goal. For instance, if a system is designed to deliver therapy within five minutes of seizure onset, the preictal state could be defined as the five-minute interval preceding seizure onset. Still, the optimal timing for intervention to effectively prevent a seizure remains unknown. As noted previously, although current neuromodulation systems (RNS, VNS, and DBS) substantially reduce seizure frequency, rates of complete seizure freedom remain low, suggesting that research should also focus on identifying the most effective therapeutic window.

7.2.2. Addressing Brain Drift

Although the challenge of developing BCIs that adapt to drift stems from the limited training data, complementary strategies are required. On the one hand, following the example of other BCIs that employ human-in-the-loop paradigms, epilepsy BCIs could incorporate periodic recalibration informed by feedback from patients, caregivers, or clinicians. Indeed, longitudinal retraining of models improved predictive accuracy in several studies [151,189,190]. On the other hand, research could focus on developing representations of brain network states that are intrinsically robust to temporal variability.

Drift constitutes a critical gap in the field hindering clinical viability, tightly linked to the lack of brain state definitions. Without robust and reproducible criteria to delineate interictal, preictal, ictal, and postictal states, addressing temporal variability in a principled and generalisable manner remains unattainable.

7.3. Performance Evaluation: A Patient-Centric Approach

A persistent methodological limitation in epilepsy-related BCIs arises from validation strategies that neglect temporal dependencies (e.g., random cross-validation or LOOCV) and fail to preserve the natural interictal–preictal–ictal–postictal proportions observed in clinical data (e.g., 80/20 or k -fold partitions). Temporal cross-validation (e.g., time-series splitting) should instead be adopted, as it more accurately reflects real-world deployment on unseen, future data. Complementary to this, Few Sample Learning paradigms, also known as *few-shot* and *one-shot learning* [191], may further enhance ecological validity. In this scheme, models are trained on a minimal subset of data (e.g., a single seizure) and tested on the remaining events within the same recording. An optimal design would integrate both principles: train the model on the first available seizure and test sequentially on subsequent seizures (Figure 2C). This approach mitigates temporal leakage, enforces chronological causality, and provides a more realistic estimate of generalisation under non-stationary neural dynamics.

In addition to adopting a universal validation strategy, most appropriate evaluation metrics should be decided for benchmarking algorithms (e.g. accuracy, F1-score, false-positive rate, or detection latency). We propose that evaluation metrics should be redefined based on patient-centred priorities. As these algorithms are ultimately intended to serve individuals with DRE, patients and their caregivers should play an active role in establishing acceptable performance thresholds. This approach resonates with the principles of Participatory Research, which are increasingly being adopted in epilepsy research

[192–196]. Although prior surveys and qualitative studies have begun identifying patient priorities, more effort is needed to translate these insights into actionable quantitative benchmarks.

7.3.1. Preferences for Seizure Detection

In the survey conducted by *Quiroga et al.* [193], it was shown that the most significant concern among patients and their caregivers is the risk of an undetected seizure, or a false negative. A high rate of false negatives compromises safety and a sense of security of seizure detection BCIs. The study also found that acceptable false-positive and false-negative rates should not exceed 25%, and that caregivers expect to be alerted within one minute of seizure onset.

7.3.2. Preferences for Seizure Prediction

Participatory Research may be particularly valuable in the context of seizure prediction, as it directly addresses the two significant challenges discussed previously: the lack of preictal state definition and standardized evaluation frameworks. Engaging patients and caregivers in the research process could help reconcile both issues simultaneously.

Surveys indicate that, regarding seizure prediction devices, the primary priorities for patients with DRE and their caregivers are achieving high predictive accuracy while minimizing false alarms. Although both objectives are essential, there is a slight tendency to prioritise sensitivity to ensure reliable seizure prediction. Patients and caregivers generally prefer short- to medium-length prediction horizons and may accept a modest increase in false-positive alarms if the device demonstrates high sensitivity, as the benefit of a timely warning outweighs the inconvenience. A trade-off may also exist between the desired prediction horizon and achievable accuracy, with users potentially accepting shorter warning times in exchange for more reliable predictions.

Given that the ultimate goal is to improve the lives of people with DRE, we propose that definitions of epilepsy brain states employed in the design of performance evaluation protocols should be grounded in patient needs and preferences.

8. Conclusions

In summary, the “therapeutic loop” framework presents a paradigm shift in the management of drug-resistant epilepsy, moving away from generalized, continuous treatment toward personalized, on-demand intervention. This review has provided a comprehensive analysis of these CLSs, addressing their limitations and proposing actionable steps to bridge the translation gap between research and clinics. While the progress in seizure detection, prediction, and stimulation technologies is promising, significant hurdles remain in achieving widespread clinical translation. The reliability of long-term seizure prediction, the validation of therapeutic efficacy, and the seamless integration of these complex systems into patients’ lives are critical challenges that require further interdisciplinary research. Ultimately, the path toward fully autonomous and effective CLSs depends on a concerted effort to refine the technology, validate its clinical utility, and ensure that the solutions meet the real-world needs of patients and caregivers, thereby holding the potential to significantly improve the quality of life for those affected by DRE.

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Abbreviations

The following abbreviations are used in this manuscript:

ASM	Anti seizure medication
aDBS	Adaptive Deep Brain Stimulation
BCI	Brain-Computer Interface
CLS	Closed-Loop System
DBS	Deep Brain Stimulation
DRE	Drug Resistant Epilepsy
ECoG	Electrocorticography
EEG	Electroencephalogram
EMG	Electromyography
eTNS	External Trigeminal Nerve Stimulation
iEEG	Intracranial Electroencephalogram
OLS	Open-Loop System
RNS	Responsive Neurostimulation System
rTMS	Repetitive Transcranial Magnetic Stimulation
SD	Standard Deviation
SEEG	Stereotactic Electroencephalogram
SOZ	Seizure Onset Zone
tDCS	Transcranial Direct Current Stimulation
VNS	Vagus Nerve Stimulation

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