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From Basic Sciences and Engineering to Epileptology: A Translational Approach

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Abstract:
Collaborative efforts between basic scientists, engineers, and clinicians are enabling translational epileptology. In this paper, we summarize recent advances presented at the International Conference for Technology and Analysis of Seizures (ICTALS 2022): 1) novel developments of structural magnetic resonance imaging; 2) latest electroencephalography signal processing applications; 3) big data for the development of clinical tools; 4) the emerging field of hyperdimensional computing; 5) the new generation of AI-enabled neuroprostheses; and 6) the use of collaborative platforms to facilitate epilepsy research translation. We highlight the promise of artificial intelligence reported in recent investigations and the need for multicenter data sharing initiatives.

Keywords: Electroencephalography; magnetic resonance imaging; hyperdimensional computing; intelligent neural prostheses; scientific platforms.

Key points:

- Advances in MRI and EEG processing are catalyzing the development of complementary tools for the diagnosis and management of epilepsy.
- Over the last few years, AI has impacted almost all aspects of epilepsy research discussed in this work.
- While the use of AI in epileptology is showing promise, larger multicenter databases are required.
- Efforts are being put towards making AI energy efficient for implantable devices including advances in hardware implementation and hyper dimensional computing.
- Scientific platforms allow to leverage the latent flexibility of digital bioelectronics and are facilitating therapy research.

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Introduction:

Translational medicine is a process-oriented discipline that intends to bring novel discoveries in basic research and industrial products into clinical applications (1). To facilitate this translation, the interaction between basic scientists, engineers, and clinicians is essential. Over the last two decades, the ***International Conference for Technology and Analysis of Seizures*** (ICTALS, http://ictals.org/) has offered a great medium for sharing and advancing knowledge related to the application of basic sciences and engineering in the context of epilepsy, which in turn has been a catalyzing force for translational epileptology (2). This work provides a non-exhaustive summary of recent advances focussing on this translation presented during ICTALS 2022, which took place in Bern, Switzerland, see Fig. 1. Novel developments of structural magnetic resonance imaging (MRI) processing methods are presented, namely in the areas of grey matter morphometry and white matter analysis. Latest electroencephalography (EEG) signal processing applications are also discussed covering both intracranial and scalp EEG recordings. We then overview current and future devices for epilepsy. More specifically, we describe how combining large numbers of patient data with artificial intelligence (AI)[1] tools can improve clinical management of epilepsy. Two examples of Deep learning (DL)[2] tools developed to learn patterns from millions of ambulatory intracranial EEG (iEEG) records from thousands of patients with epilepsy (PWE) implanted with a responsive neurostimulation device are presented. We then discuss the emerging field of intelligent

[1] Artificial Intelligence (AI) refers to the use of computer science and datasets for the development of automated algorithms for tasks that are usually associated with human intelligence. Examples include abstraction and generalization or improving after exposure to more data.

[2] Deep Learning (DL) is a subset of machine learning which entails the use of artificial neural networks composed of multiple (deep) layers.

neural prostheses including a versatile machine learning (ML)[3]-based brain state classifier and closed-loop neurostimulator. In addition, energy-efficient in-memory hyper dimensional computing is explained with applications to wearable devices and epileptic seizure detection. Finally, we discuss how collaborative platforms will play a vital role in propelling the translation of novel neurotechnologies to clinical tools.

1. Latest MRI developments:

Advances have been made to improve the analysis of MRI for epileptology. Notably, neural current imaging (3) might enable measuring field distortions due to epileptic discharges with high spatial resolution using MRI scanners in the near future. Here we concentrate on recent developments in structural MRI (see Fig. 2).

1.1 Grey matter morphometry:

Morphometric analysis of brain MRI has a long standing history in epilepsy, see (4,5) for reviews. Meanwhile, within the world-wide Enhancing Neuro Imaging Genetics through

[3] Machine Learning (ML) is a subset of artificial intelligence that involves training algorithms without explicit instructions.

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Meta Analysis consortium (ENIGMA) an epilepsy work group has been formed (6). It has identified subtle but systematic and widespread regional deviations of grey matter (GM) structure from normality in all epilepsy subtypes, affecting both hemispheres and extending far beyond the suspected pathology (7,8).

While these and earlier findings have undoubtedly contributed significantly to the understanding of disease manifestation and potentially also mechanisms, opinions on the utility of these group findings to support diagnostics in the individual were initially mixed. While specialized voxel based morphometry (VBM) analyses using T1- and T2-weighted MRI together have been presented already in 2005 (9), other researchers had more critical views (4), questioning sensitivity and specificity of VBM to detect alterations beyond visual MRI assessment. In contrast, Thesen et al. (10) have applied surface based analysis (SBA), finding that it yielded high sensitivities and specificities for detection of cortical lesions. To support the detection of focal cortical dysplasias, the Multi-centre Epilepsy Lesion Detection project (MELD) has been formed, combining SBA with AI supported approaches (11,12).

Independent from research applications, tools for individualized evaluation of volumes of lobar or sublobar cortical and subcortical GM and comparison with normative datasets have become available as commercial products focusing on epilepsy and/or other neurological disorders. Interestingly, despite availability of CE certificates and/or FDA approvals, technical and specifically clinical validation studies are still very rare (13). Goodkin et al. (14) have run a clinical evaluation study of the impact of quantitative reports (QReports) on the assessment of hippocampal sclerosis (HS), finding that they helped users with different levels of expertise to improve both, the detection accuracy of HS as

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well as the inter-rater agreement. Non-commercial approaches to support assessment of individual patient MRI with QReports have been proposed as well (15,16).

During the past five years, DL with convolutional neural networks (CNN) has become the method of choice for MRI segmentation (17). In the context of brain morphometry, CNNs have been used for high quality segmentation and parcellation of tissue types and brain regions from unenhanced or contrast-enhanced T1-weighted MRI and subsequent cortical thickness estimation (18,19). Another aspect that might turn out relevant to the application of brain morphometry in epilepsy, is the discovery of a universal and biophysically plausible scaling law of cortical folding (20). Motivated by the large degree of covariance among variables of cortical morphometry (specifically cortical thickness, total and exposed surface area), novel and mutually independent variables have been suggested and applied to epilepsy recently (21). These might turn out better suited to differentiate pathological developments than the classic variables.

1.2 White matter analysis:

Epilepsy is an archetypal network disorder. Seizures occur within and propagate across neural networks causing a myriad of stereotypical clinical presentations. White matter (WM) is recognised as a crucial component of epileptogenic networks and neuroimaging connectivity studies are increasingly revealing abnormal structural and functional interactions between networked brain regions in PWE (22), particularly cortical and subcortical hubs that demonstrate high connectivity to other brain regions (23). Neuromodulation of network hubs (24) and WM itself (25) may reduce the frequency and severity of seizures. There has therefore been increasing applications of neuroimaging

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approaches to study WM in epilepsy, particularly using diffusion MRI (dMRI). WM abnormalities are being increasingly identified in focal and generalised epilepsy disorders (26), some of which have a demonstrated histopathological basis (27).

Refractory temporal lobe epilepsy (TLE) is the most studied epilepsy disorder using dMRI approaches. Limbic WM alterations are frequently reported (26), and the distribution and extent of limbic WM tract abnormalities may account for neuropsychological impairments seen in patients with TLE (28) and may represent an imaging marker of postoperative seizure outcome (29). dMRI WM tractography methods may be incorporated into preoperative evaluation pathways, particularly for reconstruction of the optic radiations prior to anterior temporal lobectomy (30) and of eloquent tracts prior to intracranial tumour surgery (31). Despite the potential clinical importance of determining WM tract neuroanatomy and WM microstructural alterations in intractable focal epilepsy, no standardised approach currently exists for the acquisition or analysis of dMRI data for research studies or preoperative planning.

There has been an exponential increase in structural connectomic studies in the epilepsies over the past ten years with ML / DL techniques becoming more and more important (32). Whole-brain structural networks, as revealed through connectomic analysis, are perturbed in focal (22) and generalised (33) epilepsies. Among other applications, there is growing evidence indicating that the preoperative structural connectome is a sensitive marker of postoperative seizure control in patients with TLE (32,34).

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In order to be incorporated into the clinical environment, WM connectomic approaches require unambiguous and simple to interpret measures that are patient-centric and powerfully stratifying (35). Conventional diffusion tensor imaging (DTI) WM tractography is most frequently incorporated into clinical evaluation of PWE. However, these DTI approaches have fundamental limitations, which has significant implications for accurate WM tractography given that a large proportion of WM voxels contain multiple fibre orientations (36).

More sophisticated dMRI approaches increase scan time, which may present a barrier to health care pathway implementation. Still, such approaches like constrained spherical deconvolution (37), neurite orientation dispersion and density imaging (38), diffusional kurtosis imaging (DKI) (39) or fibre ball white matter modelling (FBWM) (40) are increasingly being used to evaluate patients with refractory focal epilepsy.

2. Recent advances in quantitative EEG analysis:

For decades, EEG has been considered as one of the main tools used for the care of PWE (41,42). Recent guidelines from the International Federation of Clinical Neurophysiology (IFCN) have highlighted the need for automating EEG reporting and overcoming technical barriers which is now possible due to advances in computing capabilities, engineering, and signal processing techniques (42). Quantitative EEG analysis allows extracting objective and reproducible information. Significant efforts over the last few decades have resulted in the development and interpretation of a variety of

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quantitative EEG features (univariate and multivariate; linear and non-linear) such as spectral power, chaoticity, signal complexity, cross-frequency coupling, and connectivity. This section provides a non-exhaustive review of recent advances in quantitative analysis of intracranial and scalp EEG recordings (see Fig. 3).

2.1 Intracranial EEG recordings:

In a report of the American Epilepsy Society Meeting Epilepsy Specialist Symposium, authors concluded that the use of advanced computational analysis of iEEG recordings may help better delineate the seizure onset zone (43). Authors discussed the promise of approaches based on a combination of structural connectivity and computational EEG modeling (43). More recently, subpopulations of spikes were investigated based on features such as spike rate, line length, skewness of the spike distribution, and energy for the prediction of surgical outcomes (44,45). In line with these investigations, Conrad et al. explored whether sleep and seizure-related changes in spikes allow to localize the seizure onset zone (46). Bou Assi et al. explored functional connectivity (in terms of phase locking value) during interictal spikes and showed a decrease in global connectivity (in the gamma frequency band) time-locked to the spike peak (47). Authors reported that functional connectivity was lower within the epileptic focus than outside the focus.

In contrast, Müller et al. explored the correspondence between non-linear excess interrelations (measured in terms of matrices of signal pairs' mutual information) and the occurrence of epileptiform events and found that non-linear quantitative analysis of iEEG could provide useful information during the planning of TLE surgery (48). Lundstrom et

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al. reported promising performances regarding the use of a novel interictal EEG biomarker based on spectral EEG changes (infraslow, delta, and gamma frequencies) for the prediction of mesial temporal involvement in the seizure onset zone. Authors highlighted the potential of using this quantitative biomarker along with spikes and high-frequency oscillations to guide surgical resection (49). Similarly, Stovall et al. explored whether interictal high frequency 'background' EEG (frequency range: 30-500 Hz) can be used to identify the epileptogenic zone and concluded that the concordance between the rate of high frequency oscillations and high frequency 'background' EEG features (modeled in terms of a pathology score) was a better biomarker than considering each measure individually (50).

In line with interictal iEEG investigations, Taylor et al. constructed a map of normative brain dynamics from iEEG recordings of 234 PWE that was recorded distant for their seizure onset zones, based on relative band power (51). Authors compared intracranial EEG recordings of 62 PWE to the normative map and found that, in patients with bad postoperative outcomes, non-resected regions were more abnormal than resected ones. In contrast, Smith et al. compared the performance of the epileptogenic index and slow polarizing shift index for the localization of the seizure onset zone (52). Authors found that while indices were significantly higher for contacts within the seizure onset zone, their performances depended on seizure onset patterns.

Despite significant efforts for the use of quantitative approaches within the context of neurosurgery, the variability of implantation strategies (electrocorticography, stereo EEG, mixture of both) hinders the translation of these models to a clinical setting. In a recent study, Bernabei et al. found distinct relationships in brain networks derived from stereo

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EEG and electrocorticography (53). Authors proposed methods of correction and highlighted the importance of considering the effects of spatial sampling when applying computational analyses to localize epileptic networks (53).

2.2 Scalp EEG recordings:

Recent investigations explored the use of quantitative scalp EEG analysis to assist the diagnosis of epilepsy, mainly based on the use of ML (54–59). For example, SpikeNet, a deep neural network, was trained on a total of 9571 scalp EEG records (with and without spikes) to perform spike detection and showed performances compared to those achieved by fellowship-trained neurophysiology experts (54). On the other side, DeepSpike was developed for the detection of epileptiform discharges based on multiple instance object detection and required a relatively low number of labeled training data (55). For a review regarding the use of DL for the detection of epileptiform discharges from scalp EEG, readers are referred to (59). In line with these investigations, Nadalin et al. 2021 trained a CNN for spike ripple detection based on recordings from a total of 34 subjects (60). Matos et al. 2022 proposed a classifier for supporting the diagnosis of epilepsy, based on functional connectivity features of EEG, in patients who had a first seizure (57). Thangavel et al. 2022 developed a classifier to detect EEG recordings from PWE in the presence or absence of interictal epileptiform discharges (58). Inputs to the classifier included patient age and vigilance states in addition to quantitative EEG features such as univariate temporal measures, connectivity, and graph metrics. The algorithm was tested using a leave-one-subject-out cross-validation.

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On the other side, Woldman et al. explored whether dynamic functional brain network properties of interictal scalp EEG, as measured in terms of critical coupling, onset index, and participation index allows to determine if seizures appear generalized or focal (61). More recently, Varatharajah et al. developed a classifier, based on scalp EEG, for the prediction of postoperative seizure freedom in patients who underwent anterior temporal lobectomy. Spectral features were extracted from EEG recordings and used as inputs to a Naïve Bayes classifier (62). Abou Jaoude et al. proposed a ML algorithm based on deep neural networks (HEAnet) for the detection of hippocampal epileptiform activity from scalp EEG recordings (63).

3. Current and future devices:

Beside developments in signal and image processing techniques, recent studies have investigated the possibility of integrating novel advances in AI into implantable devices for epilepsy. In the next subsections, we discuss how AI allows learning patterns from big data acquired with the NeuroPace RNS System. We then overview new generations of AI-enhanced neural prostheses as well in-memory hyperdimensional computing (HDC). This section ends by overviewing how scientific collaborative platforms can facilitate translation.

3.1 Big data to clinical tools:

Clinical epilepsy management has many challenges (64). One is the inability to accurately assess patient outcomes to treatments since patient self-reports of seizure counts are often unreliable (65). Another challenge is the lack of a systematic approach for exploring

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the settings of intervention devices like e.g. neurostimulation (66). Recent availability of large ambulatory multi-patient iEEG datasets from FDA approved neurostimulators capable of recording physiological datasets (67,68), and advances made in the domains of ML and DL have equipped the community with tools necessary for addressing these challenges (69). Over 10 million 4-channel ambulatory iEEG records from >4,000 patients have been captured from patients implanted with the NeuroPace RNS System. Applying AI techniques capable of learning patterns directly from big data to these iEEG records enable physicians to more objectively assess patient outcomes and select neurostimulator settings in a personalized, data-driven manner. Two example AI tools developed with these goals in mind are discussed below.

3.1.1 ECoG Sorter:

Hundreds of 90-second iEEG records (aka ECoGs) are typically captured from each RNS System patient between clinic visits (67). These records provide invaluable insights about the patient's epilepsy status including changes in seizure laterality and changes in the number and types of electrographic seizures. Thus, identifying stored iEEG records with electrographic seizure activity is of particular interest to physicians. Manually sorting through the iEEG records to find electrographic seizures can add substantial time to the clinical workflow and may lead to reviewer fatigue and increased human error. To aid the iEEG review process, a DL based electrographic seizure classifier ("ECoG Sorter") was developed (70). Individual channels in 138,000 iEEG records from 113 RNS System patients were manually annotated as electrographic seizures or non-seizures. The labeled datasets were used to train a series of CNN models, yielding a classification

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accuracy of 95.7% on a held-out test dataset (70). Further, the trained model's classification scores agreed with three expert physicians at the same level that the physicians agreed with each other.

3.1.2 Therapy Proposer:

When physicians make changes to a patient's neurostimulator settings, the approach to finding the next stimulation parameters is often based on their prior experience with treating similar patients (66,71). This approach is inherently biased by the physicians' recent memory, and does not leverage the experience gathered by other physicians treating similar patients. A tool that searches through large multi-site and multi-patient datasets to identify similar patients in a systematic approach may increase treatment effectiveness and shorten clinical workflows by reducing the demand on physicians to develop new programing settings for every patient. To this end, a platform was developed for identifying patients with similar iEEG patterns, seizure onset locations and lead types (72). When therapy suggestions are desired for a new patient, k-nearest neighbor's method can be used to identify iEEG records from previously treated similar patients. The search results can be further filtered to match lead types and seizure onset location with the new patient. Stimulation parameters that worked in the similar patients are suggested as settings for the new patient.

3.2 Intelligent Neural Prostheses:

Closed-loop neuromodulation is a promising therapeutic approach for medication-refractory brain disorders and could be a game changer for one third of patients with refractory epilepsy. Deployment of ML algorithms on closed-loop neural interfaces enables accurate detection of pathological brain states and rapid restoration of lost

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functions. This new generation of **AI-enhanced neural prostheses** (73,74) has recently emerged allowing precise tracking of neurological and psychiatric symptoms, while relieving latency and security concerns of conventional methods. Epileptic seizure control could greatly benefit from such intelligent closed-loop platforms. To this end, a first-of-its-kind ultra-low-power and high-density neural interface microchip was proposed featuring 256-channel ECoG/LFP recording, biomarker extraction, ML, and closed-loop stimulation capabilities, all integrated on a single chip with an active area of ~3.5mm^2 (75,76).

Existing closed-loop devices suffer from relatively low channel count (4–6) and bulky form factor and rely on simple detection methods such as feature thresholding. These issues were addressed by introducing a versatile closed-loop neuromodulation system-on-chip, the NeuralTree. While a number of recent neural interfaces have integrated ML algorithms directly on the chip (77,78), they are still limited in channel count, energy efficiency, and applicability to multiple brain disorders. The NeuralTree system was proposed to address these limitations. This microchip integrates four modules of 64-channel low-noise time-division multiplexed (TDM) mixed-signal front-ends for high-spatial-resolution neural recording. In order to extend the application of this system to a wide range of brain disorders, a rich feature extraction engine subsequently computes relevant biomarkers in the spectral, temporal, as well as phase domains (the latter is particularly useful for network-based diseases such as psychiatric and memory disorders) (79,80).

To enable on-site, real-time detection of the seizure state or other neurological conditions, this system embeds an accurate multi-class probabilistic NeuralTree algorithm with two-layer neural networks implemented in the internal nodes (81). Network pruning and weight quantization were used to compress the networks, requiring only 2.93kB of on-chip

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memory. Circuit-algorithm co-design techniques such as energy-aware regularization (76) enabled an ultra-low-energy classifier, leveraging high-density (256-Ch.) training and channel-selective (64-Ch.) inference. Overall, the combination of TDM-based sensing array, hardware-efficient biomarker extraction, and low-power ML processor enabled an unprecedented channel density in an area- and power-efficient manner.

In response to NeuralTree's detected events, a 16-channel fully-configurable high-voltage-compliant neurostimulator with passive and active charge balancing (integrated on the same chip) is triggered to suppress seizures and other abnormal activities. The chip consumes 0.227μJ/class, significantly better than existing commercial and research-based systems. The classification performance was verified on seizure and tremor detection tasks. For example, on epileptic scalp EEG (24 patients, 983 hours, 176 seizures, from the CHB-MIT dataset) and iEEG (6 patients, 596 hours, 49 seizures, from the iEEG.org), the chip achieved 95.6%/94% sensitivity and 96.8%/96.9% specificity. The system was further validated in-vivo with a 16-Ch. subdural soft μECoG array on a rat model of epilepsy. Prominent increases in spectral and temporal biomarkers and cross-channel phase synchronization at the seizure onset were observed (76).

3.3 In-memory Hyperdimensional Computing:

During their regular check-ups, PWE often receive a routine EEG recording, which is then evaluated for decisions on therapy continuation or adjustment. This appointment-based data collection, however, is severely under-sampling the highly dynamical nature of epilepsy (82). Implantable or wearable devices monitoring EEG changes and specifically seizure occurrence and timing are desirable, but require miniaturized architecture and

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energy efficient implementation of continuous signal analysis. This is where new brain-inspired ML approaches may help.

The central idea of HDC (83) is to compute with random patterns that are drawn from a very high-dimensional space. This was inspired by psychological models of human analogy processing as well as by biological central nervous systems, where information is often represented by very large spatiotemporal distributions of probabilistic neuronal population firing patterns. A key attribute of HDC is its inherent robustness to the imperfections associated with the computational substrates on which it is implemented (84). Failure in a component of hyper-dimensional random vectors is not ”contagious” to other components and failures in a subset of components are compensated by the holographic representation of memory, meaning that the error-free components can still provide a representation ”good enough” for distinction (84). HDC is therefore particularly amenable to emerging approaches in computing at low signal-to-noise ratio conditions like e.g. implantable or wearable monitoring devices. Examples include non-von Neumann in-memory computing, where the physical attributes of nanoscale memristive devices can be exploited to perform computation, leading to tremendous energy saving (85).

A primer on HDC for the iEEG seizure onset detection is provided in (82) and an application to real-time hand gesture classification from wearable surface electromyography was made in (86). This technology uses high-dimensional distributed representations and relies on the algebraic properties of its key operations to incorporate the advantages of structured symbolic representations and distributed vector

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representations. When biosignals are transformed to symbols (e.g., by using local binary patterns), they can be easily combined across many channels and over time by the HDC machinery to learn the event of interest (see (87) for more details). A number of HDC-based algorithms (88–91) were developed to operate with iEEG. One HDC algorithm quickly learns from few seizure examples (88) and generalizes well for unseen seizures, even without any false alarms on long-term iEEG dataset (89). Further, HDC leads to transparent (explainable) models that can be interpreted, for example, to automatically identify ictogenic brain regions (90), ultimately enabling post-translational support for clinical decision making.

In all these cases, the HDC algorithms directly operated with symbols or extracted features. To enable operation with raw data, it has recently been proposed to combine deep neural networks with the machinery of HDC (92). As a result, this new combination allows to quickly learn from a few examples without having the domain expert knowledge about the input modality leading to state-of-the-art performance in few-shot learning (92).

3.4 Collaborative Platforms for Translation:

The total economic cost of neurological disorders exceeds hundreds of billions of dollars worldwide per annum, yet pharmaceutical companies continue to cut investment (93–96). As previously discussed, the emerging field of bioelectronics suggests a novel alternative to pharmaceutical intervention by using electronic hardware to intelligently sense and stimulate the nervous system (97,98). In addition, bioelectronic systems might be used

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to optimize pharmaceutical doses by providing unique access to brain network dynamics, and how they respond to interventions.

Bioelectronic systems raise several challenges and opportunities when bridging the translational continuum. The considerations are multi-disciplinary and encompass basic neuroscience, regulated technology, and health care economics. Satisfying multiple demands can create significant hurdles to translation, especially when large investments over extended timeframes are required to develop the therapy.

These multiple constraints motivate new innovation models that leverage the unique capabilities of electronic platforms. For example, the flexibility of bioelectronic systems allows for the addition of implantable scientific instruments into established devices that enable novel clinical neuroscience while providing a baseline of therapy (99). The resulting scientific discoveries can then be applied to prototype new therapies. Successful prototypes are then locked into place with digital upgrades, and become the next generation's established system (100,101).

Implantable devices that serve epileptology provide illustrative examples of the scientific platform and innovation framework in practice. For example, the NeuroPace RNS system was originally designed to treat medial TLE. But with the surgical procedure established, and the flexibility of the platform accessible to researchers, the device has been used to explore novel treatments including mood disorders (102), Tourette syndrome (103), and eating disorders (104). In addition, the novel data recording has enabled new insights into both circadian and multi-day rhythmicity in seizure patterns (105), and the response of the brain networks to anti-convulsants. Similar insights are being gained with deep brain stimulation systems. The Activa PC+S (106) and Summit RC+S (107) investigational

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systems are examples where scientific instrumentation was embedded within established commercial devices. These instrumented stimulators were used in the NIH BRAIN initiative to explore advanced therapies for movement disorders (108,109), epilepsy (110), and brain machine interfacing (111). The capacity to gather extended datasets in home environments further advances our understanding of neural states, including sleep, and disease processes (112).

The attractiveness of public-private collaboration is also advancing new models for collaboration. For example, the "Picostim-DyNeuMo," is a collaborative, investigational research tool co-developed by industry (Bioinduction Ltd, Finetech Medical Ltd) and academics (113,114). The Picostim-DyNeuMo is targeting first-in-human clinical studies exploring challenging neurological disorders such as Lennox Gastaut epilepsy, chronic pain, and disorders of consciousness. Finally, the generality of the bioelectronic platform approach is further reinforced with examples including spinal cord stimulation, and diseases that extend into the peripheral nervous system including spinal cord injury and blood pressure management.

However, platforms are not without their limitations and trade-offs. Concerns include limited degrees of freedom for highly novel approaches (e.g. large channel count designs, or many leads placed in the brain). In addition, novel research systems that are not commercially supported lead to a potential risk of patient abandonment. The use of novel systems requires careful consideration of equipoise by the clinical investigator, the identification of a long-term care pathway, and transparent ethical disclosures in patient consent (115,116).

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Outlook:

This work provides a non-exhaustive overview of recent translational applications of basic sciences and engineering to epileptology presented during ICTALS 2022. We argue that novel advances in MRI and EEG processing inline with the availability of large ambulatory iEEG datasets can lead to the development of complementary tools for the diagnosis and management of epilepsy. In parallel, special efforts are undertaken to make AI energy efficient for implantable medical devices, including advances in hardware implementation and usage of paradigms novel to the field, like HDC. Novel generations of AI-enhanced neuroprostheses featuring rich biomarker extraction as well as improved channel count, per channel area, and energy efficiency are emerging. Furthermore, the development of scientific platforms that leverage the latent flexibility of digital electronics is helping catalyse therapy research. By spreading the development costs across multiple disease states and establishing an ecosystem for device implantation and research best practices, the incremental barriers for translational research can be lowered. Ultimately, the success of this strategy will be determined by improved access to novel therapies.

Indeed, the last few years have been marked by advances in AI which are impacting almost all aspects of epilepsy research discussed herein. There is a great promise for the use of AI in epileptology, given that multimodal data is gathered as part of clinical investigations. Nevertheless, databases with large sample sizes are required. Great initiatives have been undertaken to share MRI and EEG recordings and have significantly contributed to advances in the field.

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However, multicenter initiatives are required to provide standardized data acquired in different settings along with accompanying annotations and clinical information. In line with the need for multicenter datasets, in a recent editorial, Litt et al. highlighted the need for an epilepsy data sharing ecosystem and the importance of sharing algorithms as well as a lean infrastructure for benchmarking algorithms (117). Such initiatives will allow testing algorithms on independent datasets and evaluating models' out of distribution generalization. Indeed, current ML evaluations are mostly based on the assumptions that data in the training and testing sets are independent and identically distributed. However, this assumption might not always be satisfied, particularly in epileptology, where data is acquired using a variety of devices, settings, people, and time intervals, creating a domain shift between source and target distributions.

In addition, our review shows a progressive transition from traditional AI and ML investigations to the use of DL also in epileptology. Indeed, earlier AI approaches used engineered features, particularly in the field of EEG. In contrast, DL creates a mapping from raw EEG and MRI data to target outputs and doesn't require feature engineering. Instead, features suitable for the problem domain are generated by the algorithms. While recent investigations have reported promising performances and such approaches could be beneficial for epileptology, the training of DL models usually requires large amounts of data and generated features as well as decisions could be sometimes difficult to interpret. Given that translation requires an interdisciplinary understanding, interpretability should be considered in the design and validation of novel algorithms.

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Over the last two decades, the ICTALS community has demonstrated the importance of collaboration between basic scientists, engineers, and clinicians for the translation of novel discoveries in basic research and industrial developments to epileptology. We believe that latest advances in AI combined with interdisciplinary expert knowledge will open the door to novel diagnostic and treatment avenues for people with epilepsy.

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Figure Legends:

Fig. 1. Overview of recent advances in translational epileptology. MRI: Magnetic resonance imaging; EEG: Electroencephalography.

Fig. 2. Examples of quantitative grey and white matter analysis of brain MRI used in epilepsy research. Morphometric measures derived from T1-weighted MRI (middle left) used to identify atypical brain features in epilepsy cohorts (bottom left) are shown in the left of the figure, including cortical thickness, curvature and surface segmentations (surface ROIs). Examples of white matter measures derived from diffusion-weighted MRI (middle right) used to examine brain network alterations associated with epilepsy (bottom right) can be seen on the right. These include metrics such as fractional anisotropy, whole brain tractography, tract shape features and metric variation along tracts.

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Fig. 3. Automated analysis of scalp and intracranial EEG to predict clinical outcomes.
A: The raw EEG is acquired and segmented into shorter epochs. The epoch size relates to the timescale of the neurophysiological process being exploited.
B: A traditional ML pipeline. The EEG is preprocessed (filtering, artifact correction, channel interpolation). Features are then extracted from the processed signal, such as interictal spike morphology and rate, functional connectivity between brain regions, or power spectral density estimated via time-frequency analysis. The features are used as input to a traditional machine learning model.
C: A deep learning pipeline. Here, the raw EEG is input into a deep neural network (such as a convolutional neural network in the figure). The important features are then learned by the model instead of requiring to be pre-specified by the engineer.
D: The ML pipeline is optimized to predict a specific clinical outcome. The final model is usually tested on a new set of EEGs, and its predictions are compared to the ground truth to assess the model's performances.

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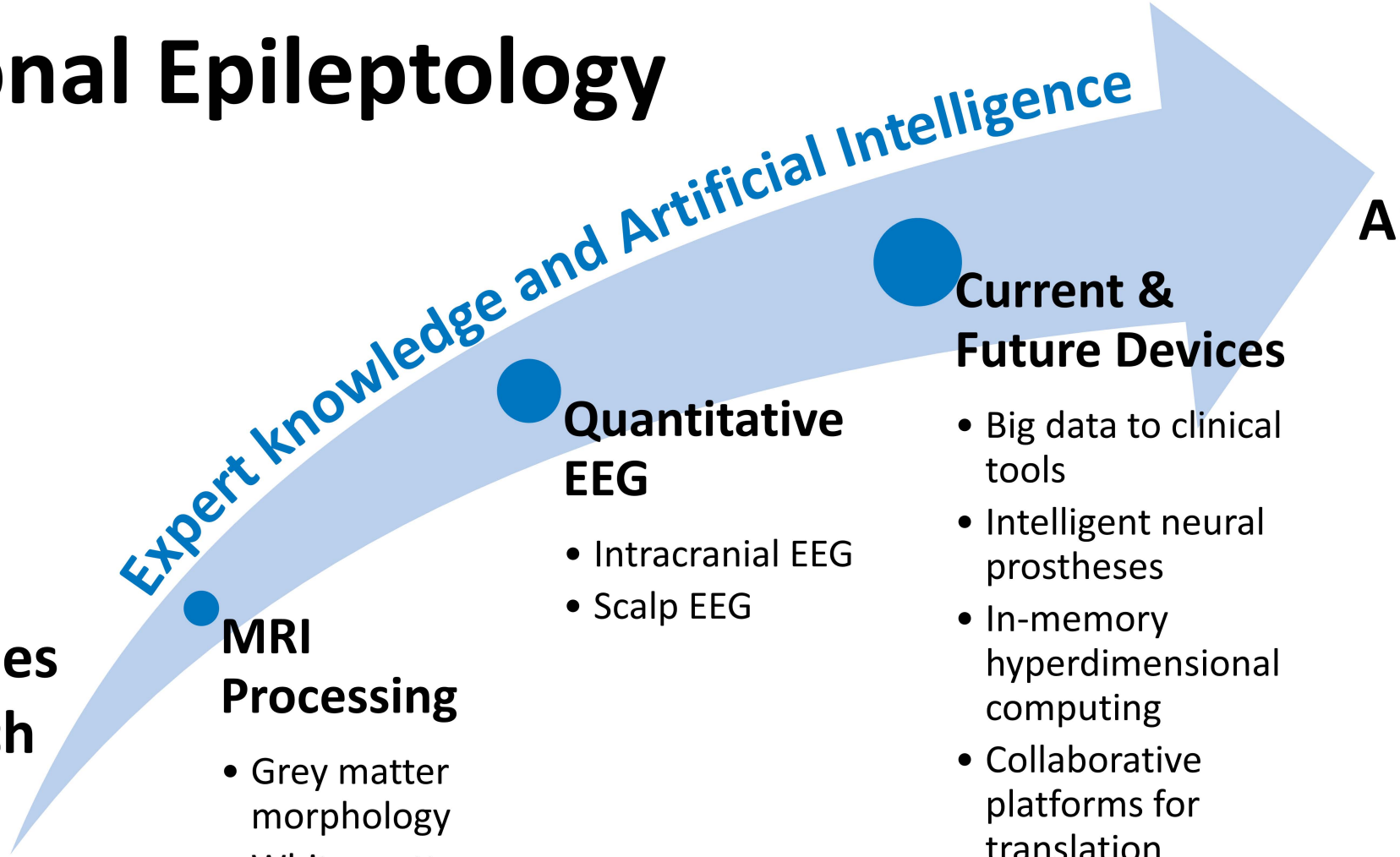
Translational Epileptology



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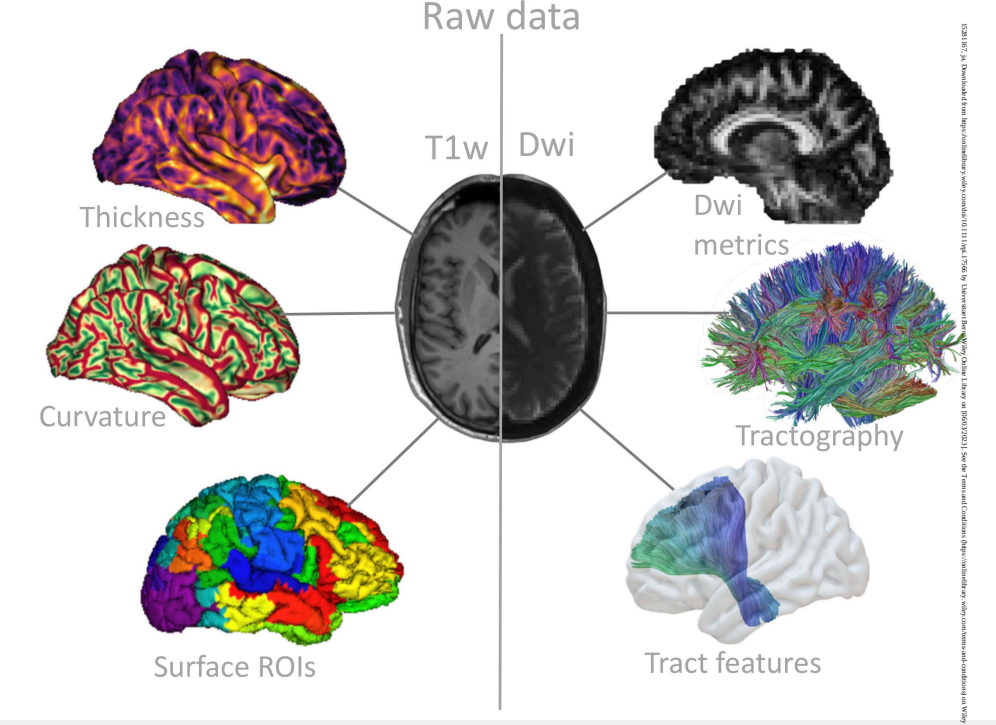

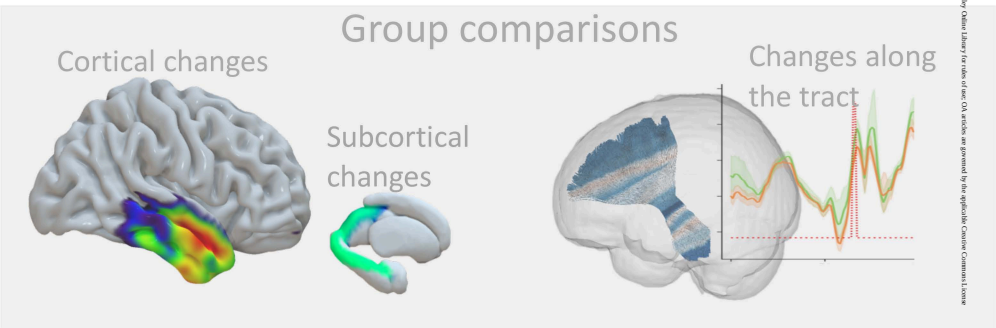

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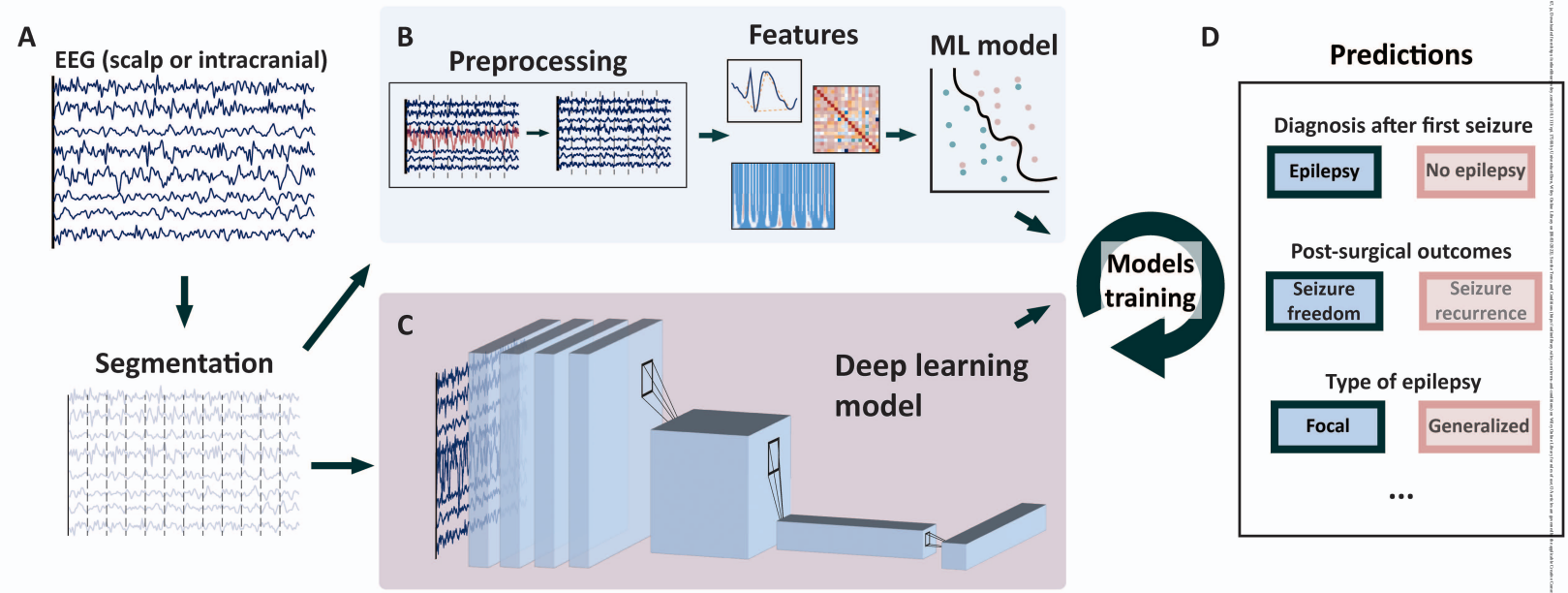
A
EEG (scalp or intracranial)
Segmentation
B
Preprocessing
Features
ML model
C
Deep learning model
Models training
D
Predictions
Diagnosis after first seizure
Epilepsy
No epilepsy
Post-surgical outcomes
Seizure freedom
Seizure recurrence
Type of epilepsy
Focal
Generalized
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