REVIEW

Big Data in Epilepsy: Clinical and Research Considerations.

Report from the Epilepsy Big Data Task Force of the International League Against Epilepsy

Samden D Lhatoo MD FRCP (Lon) [1], Neda Bernasconi MD PhD[2], Ingmar Blumcke MD PhD[3], Kees Braun, MD PhD[4], Jeffrey Buchhalter MD[5], Spiros Denaxas PhD[6], Aristea Galanopoulou MD PhD[7], Colin Josephson MD MSc[8]., Katja Kobow MD PhD, [9] Daniel Lowenstein MD PhD[10], Philippe Ryvlin MD PhD[11], Andreas Schulze-Bonhage MD PhD[12], Satya S. Sahoo PhD, [1] Maria Thom MD PhD[13], David Thurman[14], MD MPH, Greg Worrell MD PhD[15], Guo-Qiang Zhang, PhD[1], Samuel Wiebe MD MSc[8].

[1]University of Texas Health Sciences Center at Houston, Houston, Texas, USA.

[2]Neuroimaging of Epilepsy Laboratory, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada

[3]Friedrich-Alexander-University Erlangen-Nürnberg, Universitätsklinikum Erlangen, 91054 Erlangen, Germany

[4]Department of Child Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, the Netherlands

[5]Department of Neurology, St Joseph's Hospital and Medical Center, Phoenix AZ

[6]Institute of Health Informatics, University College London, NW1 2DA, London, United Kingdom

[7]Saul Korey Department of Neurology, Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, 1410 Pelham Parkway South, Kennedy Center Rm 306, Bronx NY 10461, USA

[8]Department of Clinical Neurosciences, University of Calgary, Canada

[9]Friedrich-Alexander-University Erlangen-Nürnberg, Universitätsklinikum Erlangen, 91054 Erlangen, Germany

[10]Department of Neurology, UCSF, San Francisco, CA

[11]Department of Neurosciences, University of Lausanne, Switzerland

[12]Epilepsy Center, University Hospital Freiberg, Germany

[13]Institute of Neurology, University College London, UK

[14]Emory University, Atlanta, GA

[15]Department of Neurology, Mayo Clinic, Rochester, MN

Address for Correspondence: Samden Lhatoo,

Texas Comprehensive Epilepsy Program, University of Texas Health Sciences Center, Houston, Texas 77030, USAslhatoo@aol.com

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Epilepsy is a heterogeneous condition with disparate etiologies, phenotypic and genotypic characteristics. Clinical and research aspects are accordingly varied,

ranging from epidemiological to molecular, spanning clinical trials and outcomes, gene and drug discovery, imaging, electroencephalography, pathology, epilepsy surgery, digital technologies and numerous others. Epilepsy data is collected in the terabytes and petabytes, pushing the limits of current capabilities. Modern computing firepower and advances in machine and deep learning, pioneered in some diseases, open up exciting possibilities for epilepsy too. However, without carefully designed approaches to acquiring, standardizing, curating, and making available such data, there is a risk of failure. Thus, careful construction of relevant ontologies, with intimate stakeholder inputs, provides the requisite scaffolding for more ambitious big data undertakings, such as an epilepsy data commons. In this review, we assess the clinical and research epilepsy landscapes in the big data arena, current challenges and future directions, and make the case for a systematic approach to epilepsy big data.

Key words

Big data, epilepsy, epilepsy ontology, epilepsy informatics

Bullet points

- Epilepsy data is multi-modal, and requires big data principles for proper handling.
- Big data approaches provide both clinical and research opportunities.
- Structured and principled approaches to epilepsy big data is necessary for maximum impact

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Introduction

Big Data is an intuitive, colloquially used term [1] – first in business, and latterly in science and healthcare. MetaGroup's 2014 definition describes Big Data as high-**volume**, high-**velocity** and high-**variety** information assets that demand cost-effective, innovative forms of information processing for enhanced insight and decision making. In addition to these "3Vs", [2] the fourth "v" of data **veracity** is particularly pertinent since suspect data draws suspect conclusions. (Figure 1) In an era of unprecedented collaboration and resource pooling, Big Data's promise is both inviting and challenging, especially in epilepsy due to its inherent heterogeneity and the vast array of scientific disciplines it involves. This review examines Big Data aspects specific to epilepsy, and describes current state of the art as well as future directions.

The Meaning of Big Data

In epilepsy, a plethora of disparate data drives **variety** (phenotype, genotype, video-EEG, extra-cranial and intracranial physiological signal, structural and functional imaging, metabolomics, wearables), which in turn drives **volume** (currently terabytes), challenges **veracity** (data acquisition, standardization) and highlights current deficiencies in managing data generated with high **velocity**. (Figure 1) However, as Big Data becomes increasingly commoditized, it may be more helpful to think of "Big Data" as a frame of mind. This allows perception of the scientific landscape in a more ambitious data scale, and enables bigger questions. In order to

scale and accelerate scientific progress, a Big Data frame of mind drives research in three new directions.

1) Collaboration. The last century has seen tremendous progress in healthcare delivery and research, using traditional approaches, whether pharmaceutical randomized controlled trials, or basic science. The field however, is poised to enter a new era enabling unprecedented collaborative possibilities. The sudden unexpected death in epilepsy (SUDEP) exemplar, illustrates Big Data opportunities. Here, identifying a sufficiently powered cohort of patients requires meticulous, prospective follow up of large at-risk cohorts in the Epilepsy Monitoring Unit (EMU). [3] Multiple EMUs collaborate, generating several hundred gigabytes of data per patient. The Epi25 (genetics - see http://epi-25.org) and ENIGMA (neuroimaging - http://enigma.ini.usc.edu/ongoing/enigma-epilepsy) are examples of similar highly successful, domain-specific collaborations which allow for validation of promising ideas at an accelerated pace.

2) Data resource infrastructure (a.k.a. data commons). New challenges emerge as soon as data are put in the hands of a community of investigators, rather than in individual laboratories. The 2010 Institute of Medicine (IOM) report, [4]"Elements of an Integrated National Strategy to Accelerate Research and Product Development for Rare Diseases," recommended a national strategy that "shares research resources and infrastructure to make good and efficient use of scarce funding, expertise, data, and biological specimens." This recommendation is especially

relevant to the epilepsy community and underscores the needs to make data Findable, Accessible, Interoperable, and Reusable (the FAIR principles).[5]

The NIH Data Commons (or Commons) aims at a shared virtual space for digital objects to be found, stored, commented and computed upon by the scientific community. Four components are considered integral parts of the Commons: a computing resource for accessing and processing digital objects; a "digital object compliance model" that enables digital objects to be FAIR; datasets adhering to compliance model; and data access services. An Epilepsy Commons, following the sleep exemplar,[6] would greatly facilitate epilepsy research, enhance the efficiency of resource utilization, and ensure the rigor and reproducibility of epilepsy research.

3) New modes for interacting with waveform data. A Big Data vision requires new modes management of datasets generated from epilepsy research. One such opportunity is the signal data format called the "File Wall" Challenge. Because simply expanding storage or adding computing power will not cope with the volume and data complexity, data organization challenges must be addressed. In existing cloud storage/processing systems large signal datasets are typically stored as identified unstructured "blobs." Traditional distributed file systems present "file wall" barriers that make data access, transmission, processing and analysis more difficult. There is an immediate need in epilepsy for research into ontology-driven, cloud-based data representation and management methods. Several initiatives have begun to address multimodal interaction including the Brain Imaging Data Structure (BIDS - https://bids.neuroimaging.io) and Fast Healthcare Interoperability Resources (FIHR

- https://www.hl7.org) that may extrapolate to epilepsy. A significant challenge with waveform data currently lies in a neurophysiological data format that allows interoperability of video-EEG data. The Multiscale Electrophysiology Format version 3 (MEF3) is one format that has been proposed as a universal standard, addressing an urgent need in both research and clinical domains, allowing easy exchange of data. [7] There is also an increasing shift towards machine learning, deep learning and artificial intelligence in epilepsy big data, particularly in its EEG aspects.[8] These include EEG spike detection, and automated surface EEG and intracranial EEG seizure detection, some of which already have impactful clinical applications such as with closed loop Responsive Neural Stimulation.

4) Data safety and privacy. Increasing data innovation creates inevitable conflict with informational privacy. The application of Fair Information Practice Principles (FIPPs) is paramount, and include individual control, transparency, respect for context, security, access and accuracy, focused collection, and accountability. These are challenged by big data paradigms, and careful attention to existing regulations (from institutional review boards to national regulations, e.g. Health Insurance Portability and Accountability Act [HIPAA]) is essential. For example, there is increasing recognition that data de-identification and anonymization are not the silver bullets to data privacy issues they once were. Nowhere is this more relevant than in the genomics arena data where subject “re-identification” is a major concern[9], and as yet incompletely addressed in the legal arena.[10]

Getting the Basics Right – Epilepsy Ontology, Classification and Common Data Elements

Biomedical ontologies are widely used to achieve three data management objectives: (1) management of multi-dimensional knowledge; (2) integration of disparate data; and (3) automated reasoning for decision support and knowledge discovery [12]. For example, the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) is one of the most comprehensive and widely used biomedical ontologies that serves as the de-facto standard for encoding clinical information in electronic health record (EHR) systems. SNOMED CT together with several other biomedical ontologies, such as the Human Phenotype Ontology (HPO), RxNorm Gene Ontology are predicted to have a central role in clinical Big Data applications, including data-driven classification of diseases as part of the precision medicine initiative [13]. Formal languages for modeling are used, such as the Ontology Web Language (OWL) based on description logic [14]. OWL-modeled ontologies, accurately model a *domain of interest* and support the use of automated tools called 'reasoners' to discover implicit knowledge from a big data repository. An ontology structure is inherently a knowledge graph which can be used to infer implicit knowledge from large datasets.

The generic informatics definition of ontology is "a formal specification of terms in the domain *(e.g. epilepsy)* and relations among them *(e.g. focal impaired awareness seizure is a type of focal seizure which is a type of seizure)"*. One key feature is the multi-axial categorization of a concept, which enables it to be applied to various

organizations of information within that domain. This significantly simplifies tasks of organizing and exploring large datasets. Ontology-supported queries together with reasoning tools allow users to explore hitherto undiscovered knowledge about how data relates to each other.

Multiple ILAE classification & terminology task forces and work groups have been challenged by the complexities inherent in characterization of seizures/epilepsies. The factors that require consideration have included: locus of onset, location, propagation, age of onset, age of remission, prognosis, EEG and neuroimaging characteristics, biological mechanism, etiologies, co-morbidities and functional impairment. Even as the need for multiple axes has been appreciated, several 'structural' issues contribute to the classification problem. These include (1) lack of standardized definitions for core terms (concepts); (2) the evidence-base to determine how these various factors relate to each other; (3) the reality that information available in one setting may not be available in another; and (4) use of uni-axial classification hierarchies that by their structure do not easily allow a term in one branch of a classification to be incorporated into another. The need for 'assembly' of various concepts in different hierarchies (e.g. based upon age of onset) for different purposes (e.g., clinical care, epidemiology) has been recognized [15, 16], but implementation has been impeded due to lack of a computable modeling framework such as OWL.

Currently, there are three public domain seizure/epilepsy ontologies available, hosted by the NIH-funded Bioportal site (URL). We discuss two. The Epilepsy

Syndrome Seizure Ontology (ESSO) was the first attempt to harmonize existing seizure/epilepsy classifications to allow common definitions, but most importantly to enable organization by available information. Starting with semiology, demographic and testing (EEG, genetic testing) factors can be added if known (Figure 2). Another robust example is the Epilepsy and Seizure Ontology (EpSO) that models multi-dimensional information including seizures, seizure features, etiology (including gene IDs mapped to Gene Ontology [11], and drug information). EpSO (Figure 3) is currently used in a variety of informatics tools [17-26].

Like all disruptive technologies, the concepts related to ontologies and OWL will require education and familiarity prior to adoption in epilepsy that can lead to meaningful basic and clinical experiments. Challenges for adoption include: (1) consensus on meanings of terms (concepts) (2) evidence to provide connections (relationships) between terms and (3) the necessity for the epilepsy community to embrace the reality that knowledge related to epilepsy is truly multi-dimensional, requiring harmonization of its various components. Just as gene sequencing is now considered essential for diagnosis, so will ontologies be for understanding epilepsy.

Big Data in Intracranial EEG (IEEG) Research

IEEG recordings provide a window on to mechanisms of brain function with unique temporo-spatial resolution. For study of electrophysiological activity, access to databases providing IEEG recordings is critical. Recordings with high numbers of

multi-contact electrodes with an extended frequency range for local field potentials and single neurons require databases that integrate data at rates of up to a TB per day. Useful analyses require valid, extended metadata e.g. behavioral data, electrode positions in relation to individual brain structures.

The seizure prediction field highlights the need for large datasets; early results based on limited datasets [27, 28] suggested that forecasting was infeasible, whereas later, extensive dataset studies provided the key to success [29]. These efforts [30, 31, 32, 33] provide examples of databases that use long-term recordings based on local servers (EU) or commercial cloud services (US).

Increasingly, centers are offering shared clinical and research datasets [34, 35]. Furthermore, multinational collaborations are establishing databases on specific EEG datasets, one example being the F-TRACT-database joining information from intracranial evoked cortico-cortical potentials from 25 European centers to build a network of functional connectivity [36].

Whereas some technological challenges inherent to data format variability appear solvable, others remain unsolved, including different country-based data safety standards, willingness to share not only data but also algorithms for re-validation, and sustainable funding for maintenance and development beyond project level [33].

Neuropathological Repositories and Big Data

Biorepositories should not only offer long-term storage of human brain and blood samples, but also catalog a standardized set of data describing the patient's clinical history and phenotype. Up-to-date patient consent and ethical approval must be in place to allow sharing of biological samples and research data. However, most tertiary epilepsy centers in Europe will select less than 50 patients a year for epilepsy surgery.[37, 38] Very large tertiary centers may operate on more than 150 patients a year.

The European Epilepsy Brain Bank consortium (EEBB)_was established in 2006 as a virtual database aiming to standardize histopathological reporting of specimens obtained during epilepsy surgery and epileptogenic brain lesions [39]. To date, EEBB has collected diagnoses from 9523 children and adults from 36 epilepsy surgery centers in 12 European countries and prompted the ILAE to develop an International Classification of Focal Cortical Dysplasia [40], of hippocampal sclerosis [41] as well as international recommendations for the histopathological work-up of epilepsy surgery specimens. [42] Disease classifications help to define a disease and also inform surgical patient management, where decision making may still rely on small series and randomized trials for difficult-to-treat focal epilepsies. [43, 44]

Under the direction of the 7th European Health Framework Program (FP7), EEBB was promoted in 2014 as a biorepository to support clinical trials in epilepsy surgery. The European Union (EU) framework program Horizon2020 promoted EEBB as a European neuropathology reference center. The biorepository includes long-term

storage of paraffin-embedded and fresh frozen brain samples, and matched blood samples with minimum de-identified clinical data.

Limitations of this dataset include its retrospective nature, inability to predict surgical outcomes, medication use, EEG and MRI biomarkers. The database is encrypted into the web-based SecuTrial platform, which does not allow connection with biomedical OMICs. International collaboration and data sharing is restricted to partners of the FP7 consortium. These limitations endorse an ILAE mandate to promote international collaboration for big data analysis of human epilepsy brain samples and harmonization of written patient consent, ethical review and material transfer agreements.

Epilepsy Imaging and Big Data

Magnetic resonance imaging (MRI) allows for comprehensive analysis of the whole brain. This technique can provide detailed descriptions of structure, function, metabolism and networks, from single cells to systems in models and humans, which parallels the scope of the genome and other biomes.

In epilepsy, a leading example of collaboration is the Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA) project based on meta- and mega-analyses. Launched in 2015, ENIGMA-Epilepsy uses harmonized quality checks rather than sharing datasets across an international consortium of more than 50 sites and it has already produced insightful results [45]. Notably, this approach

bypasses challenges related to institutional ethical approvals and the need for high throughput computing. Other sharing strategies currently not used in epilepsy rely on sharing raw imaging data in repositories, such as the NIH-funded Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC - www.nitrc.org), a suite of services including a registry, image repository, and a cloud-based environment.

Beside ethical concerns, data science faces other challenges. For example, variability in clinical assessments, missing data and variable study cohorts may confound disease severity with study site. A major technical challenge relates to variability in MRI hardware and acquisition, image quality, and parameters, which may lead to differences in data scaling and noise. A mitigation strategy would be the adoption of the newly-proposed Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MRI) protocol entailing a set of acquisitions readily available on most MR scanners.[46] It is crucial to establish and abide by MRI quality-standards and to append standardized phenotypical descriptors based on the most recent classifications. Disease models using multi-centric MRI data require consideration of confounders related to unbalanced patient-to-control ratios and measurement variance across sites. A solution would be to first develop models based on a given dataset and test generalizability to others, rather than prioritizing pooling data across sites.

Epilepsy Genetics and Big Data

Collective genomic efforts in the past decade, have capitalized on access to high-throughput genomic analysis and next-generation sequencing, as well as team science, which fosters collaboration and scaling of studies that would never be possible by single investigators. A critical element has been the collection of detailed phenotypic information in addition to other data (e.g. EEG records, source documentation from medical records, etc.).

The NIH funded Epilepsy Phenome/Genome Project (EPGP), is an international, collaborative study that collected detailed phenotype data and DNA samples on over 4,100 subjects (and family members) with specific forms of epilepsy. The repository with millions of data points continues to be fully operational for follow-up studies. [47, 48] The EPGP cohort, along with European and Australian datasets, were critical to the success of the NIH-funded Epilepsy Center Without Walls entitled "Epi4K: Gene Discovery in 4,000 Epilepsy Genomes", which utilized exome sequencing to identify new *de novo* variants causing epileptic encephalopathy and Lennox-Gastaut syndrome, and ultra-rare genetic variation in common forms of epilepsy, among other findings. [49, 50] Other examples include the large datasets created through the International League Against Epilepsy Consortium on Complex Epilepsies,[51] the EuroEPINOMICS-RES Consortium,[52] and the massive, international effort currently underway, entitled Epi25, that has a goal to sequence 25,000 epilepsy exomes (see http://epi-25.org/). Encompassing epilepsy and more, the database of Genotype and Phenotype (dbGaP) is an NIH maintained database of datasets, which archives and distributes results of studies investigating genotype-phenotype interactions.[53]

The explosion in knowledge of genetic variants associated with human epilepsies and in molecular targets for ictogenesis, epileptogenesis, and comorbidogenesis constitute rich libraries to search for candidates in molecular pathogenesis and therapy. In animal studies, concerted efforts to generate knockout[54] or conditional knockout mice [55],[56],[57] and C57 embryonic stem cells have resulted in at least 17,000 knockout mice. Characterization of the phenotype of these genetic models[58] will be offered in a public access database. While this is invaluable for investigators, significant enhancements will be needed to include endpoints relevant to clinical epilepsy research.

The ILAE/AES Joint Translational Task Force, in collaboration with NINDS is generating preclinical CDEs for epilepsies and comorbidities to facilitate data input from multiple labs into big databases,[59] generate accepted classifications and terminologies for video-EEG studies and seizures in rodents,[60-64] and perform systematic analyses of preclinical studies.[65] An aim is to optimize these products in platforms that could be used in big databases to enhance epilepsy research, including translation from preclinical to clinical arenas.

"Relatively big data" from multicenter cohort studies

Sharing and assembling results from single-center cohorts through collaborative research efforts has increasingly been applied to address questions in epilepsy. Although these approaches do not comply strictly with definitions of big data, a 2016 Lancet Neurology "round-up" comment used the term big data when referring to

multicenter cohorts of 1450 surgical patients, 446 children with absences, and as few as 14 neonates. [66] The cooperation of many dedicated physicians from different centers was considered the *key attribute to new research in epilepsy*.

For rare epilepsies, small or heterogeneous populations, and for new, unproven therapies, pooling results from small cohort studies can yield relatively "big data", overcoming their lack of statistical power and sources of bias. Multicenter cohort studies or meta-analyses have merits, even when the quantity of data is much smaller than in big data. In Europe, the European Reference Network EpiCare (http://epi-care.eu/)serves to facilitate multinational collaborations in rare and complex epilepsies. For focused research questions, limited but specific and well-structured "clean" data can be systematically collected retrospectively from available multicenter patient data, enabling multivariable analyses and prediction modeling with sufficient statistical power. For example, the *TimeToStop* cohort study allowed to investigate whether early withdrawal of antiepileptic drugs (AED) after pediatric epilepsy surgery is safe. [67] One researcher collecting data systematically from 766 children across fifteen collaborating centers ensured high-quality data and found that early AED withdrawal did not affect seizure outcome. [67]

Alternatively, published single-center cohort studies can be meta-analyzed with either aggregate or individual participant data (IPD). Although IPD is the gold standard for clinical research synthesis [68] retrieval rate is sub-optimal [69], and it is still underutilized. Nevertheless, IPD meta-analyses have increasingly been applied in epilepsy, for example to determine AED monotherapy efficacy [70], predict seizure

outcome after epilepsy surgery in tuberous sclerosis complex [71], calculate the chance of seizure recurrence after a first febrile seizure [72] and the risk of ictal asystole in epilepsy [73], and to produce a prediction model that calculates the individualized risk of seizure relapse following AED withdrawal. [74] Big data research, multicenter cohort studies and IPD meta-analyses can be considered complementary approaches.

Electronic Health Records and Epilepsy Big Data

Data from Electronic health records (EHR), generated during routine clinical care across multiple settings,[75] are increasingly being linked [76] and used for translational research and for large-scale observational research. EHR data can be classified into three main types [77]:

a) *Structured* data: Mostly used for administrative purposes and annotated using controlled clinical terminologies and statistical classification systems such as SNOMED_CT, ICD-10, LOINC and RxNorm. These typically include information such as diagnoses, prescriptions and surgical procedures and interventions during in-patient and out-patient care.

b) *Unstructured* data: Recorded as raw text and typically include a patient's medical history, and clinicians' observations and findings.

c) *Binary* data: Traditionally include data from imaging procedures and increasingly from personal healthcare wearable devices or smart phones.

Research platforms such as CALIBER[78] link EHR data from primary care, hospital care and mortality and offer researchers high resolution longitudinal data on chronic and acute conditions at a population level. Raw EHR data, however, suffer from multiple challenges [79] and require substantial preprocessing before they can be research-ready for statistical analysis, a process known as *phenotyping* [80] [81].

In the context of epilepsy research, curated EHR data offer substantial advantages compared to traditional methods: a) EHR have large sample sizes, enabling scientists to gain accurate measures of incidence and prevalence in populations; b) Linked EHR can be utilized to quantify healthcare utilization and costs associated with epilepsy, its treatment and comorbidities; c) high-resolution EHR data can help identify and validate novel epilepsy subtypes using unsupervised machine learning, which can lead to personalized medicine approaches; d) Longitudinal EHR data can help characterize valid phenotypes of disease progression, with unique etiological and prognostic features.

Epidemiological Opportunities in Big Data

Clinical epidemiological data in the zettabyte (10^{21} bytes or 1 trillion gigabytes) [82] range, representing a large portion of the population of interest, is particularly apt for Big Data applications, and can detect small but clinically meaningful effect sizes. Such unprecedented statistical power can confer immense precision. However, unless the veracity of the data is ensured, narrow confidence intervals can be erroneously misconstrued as accuracy [83].

Data sources and validation

Large clinical data repositories need not be population-based, but they must be representative of the population of interest. Typically, population-based sources include administrative health data, EHR data, national health surveys, and vital statistics (Table 2). Non population-based platforms include national and regional clinical registries [84-86] and pooled individual patient data from clinical trials [69]. Frequently, there is a trade-off between granularity and quality. For instance, clinical registries and pooled trial data are frequently rich and detailed but can have selection bias (trials), and may lack consistency and completeness (voluntary registries).

Valid case definitions for epilepsy now exist for administrative health records [87] and EHR [88, 89]. Although the reported sensitivity and specificity are high (>80-85%) [87, 88], these are often context-specific, and their utility should be quantified when used in different datasets [90]. Likewise, outcome measures, if not validated, can lead to spurious conclusions [91]. Thus, all conditions of interest must be treated with methodological rigor lest results become irrevocably skewed due to misclassification bias.

Analyses from validated epidemiological data have yielded remarkable insights into the incidence [92, 93] and prevalence [92, 94] of epilepsy, the co-morbid profile of epilepsy [94], the bi-directionality of depression and epilepsy [95, 96], the association between epilepsy and autism [97, 98], and debunking the spurious putative link between antiepileptic drug use and suicide [99, 100]. Overall mortality [101, 102] and SUDEP [101, 103]

have been studied with large EHR and administrative data. Initial endeavors at applying machine learning to Big Data for the purposes of predicting epilepsy outcomes appear promising [104]. Finally, population-based surveillance of health care access, utilization, and costs are now permissible using these large data sources [105, 106].

Used prudently, hitherto unforeseen opportunities exist for cost-effective and statistically powerful investigations into the epidemiology of epilepsy using big data. These include disease surveillance, identification of new somatic and psychiatric conditions, precision medicine targets, and health outcomes and health care use assessments. However, many of these hypothesis-generating studies will require validation through other methods.

Digital Health, Wearable Technology and Big Data

Over 5 billion human beings currently use a mobile phone, the majority of whom share information on social media. In 2017, close to half of the population used at least one connected care technology to monitor health indicators (Future Health Index 2017, Philipps). US hospitals and insurance providers are rapidly transitioning to digital mobile health (mHealth). Concurrently, partnerships between large IT companies (e.g., Apple, and Google) and hospitals, are developing novel healthcare ecosystems. Hence, there is huge potential for information technologies to generate big data in any medical field, provided relevant data can be captured and shared.

Most interestingly, connected devices with sensors have already proved useful for detecting generalized tonic-clonic seizures (GTCS)[107-112] , and some of these have received FDA approval (e.g., Embrace, Brain Sentinel).[113, 114] Others are being developed from non-medical mainstream wearables (e.g., Apple watch), offering potential for major dissemination within the epilepsy population.[113]

GTCS can be reliably detected with sensors measuring body movements during the clonic phase (wrist accelerometer or pressure bed sensor),[115-118] surface electromyography of the arm during the tonic phase, [119-121] and changes in electrodermal activity.[114, 122] Changes in heart rate, that can be extracted through photoplethysmography,[123, 124] can also be used to detect various seizure types.[125, 126] Recently developed multimodal seizure detectors are likely to prove more sensitive and specific than any single-sensor technology.[127-129]

Detecting GTCS with connected devices can enable more precise evaluation of seizure frequency and treatment optimization, as well as timely intervention by triggering alarms. This might help reduce seizure-related adverse events and fatalities.[130, 131] Data gathered through connected devices may also provide biomarkers of various comorbidities, e.g., AED side effects, risk of SUDEP, and seizure-modulating environmental and internal factors. As already demonstrated by the North-American Brain Initiative and European Human Brain Project, mHealth (mobile health) data are considered complementary to –omics in precision medicine.

This rapidly developing field faces important challenges, including data privacy and merging information from connected devices, usually stored on generic clouds, to EHRs managed by health providers. The research potential of mHealth technologies in epilepsy should be facilitated by the unique collaboration developed by the ILAE and International Bureau for Epilepsy (IBE).

Big Data Funding Initiatives in Medical Research

Recognizing the transformative opportunities provided by Big Data, government funding agencies around the world have launched strategic programmatic investment to accelerate Big Data research as highlighted below..

EU: Horizon 2020 is the leading EU Research and Innovation program (with nearly €80 billion of funding available over 2014 to 2020). Funding opportunities under Horizon 2020 Programme (https://ec.europa.eu/programmes/horizon2020/) include topics such as “Big Data technologies and extreme-scale analytics” (ICT-12-2018-2020) that are focused on data management, data processing, deep analytics, data protection, data visualization, and user experience.

United States(US): In the US, the flagship program has been BD2K, Big Data to Knowledge, a trans-National Institutes of Health initiative launched in 2013 to support the research and development of innovative and transformative approaches and tools to maximize and accelerate the integration of big data and data science into biomedical research. New data science strategy (https://datascience.nih.gov)

includes Precision Medicine and the BRAIN initiative, with the National Library of Medicine (NLM) as the nexus of data science resources. The US National Science Foundation (NSF), another federal funding agency of US, has a standing program on Critical Techniques, Technologies and Methodologies for Advancing Foundations and Applications of Big Data Sciences and Engineering. “Harnessing Data for 21st Century Science and Engineering” has been identified as one of the 10 Big Ideas for Future NSF Investments (https://www.nsf.gov/about/congress/reports/nsf_big_ideas.pdf).

China

Big Data funding initiatives in China has been represented by investment in Precision Medicine. Precision Medicine is a part of the Chinese government’s Five Year Plan for 2016-2020 as it works to prioritize genomics to drive better health care outcomes. Investment through programs such as the National High-Tech R&D Program has led its investigator community and infrastructure to the forefront of research involving methodologies of genomics and proteomics, with rapid development in technologies for molecular imaging, drug targets and big data.

The role of the ILAE Task Force for Big Data

The digital revolution has opened up tremendous opportunities for large scale collaborative epilepsy clinical care and research. The ILAE Big Data Task Force comprises epilepsy clinicians and researchers who are engaged in disparate epilepsy research domains and have an interest in large-scale collaborative clinical and research endeavors. Their role is to review past and current epilepsy big data

efforts, and over the tenure of the Task Force, to recommend guidelines and advice that help deliver high impact Big Data research that is directly relevant to patient care, while providing a framework of reference for navigating privacy, legal, and ethical issues surrounding such enterprises. Specific laws, such as the General Data Protection Regulation (GDPR) in Europe and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) in the USA govern such endeavors.

Conclusion

Big data, data sharing and high-performance computing are poised to restructure the way we deliver health care and do research. An overview of these themes in epilepsy shows great opportunities and important challenges. Successful instances where these processes produce new and important knowledge are beginning to emerge and should be strengthened. To harness the full potential of big data will require attention to policies and procedures, secure environments, data quality standards, data platforms, and data science models that can accommodate the large volume and variety of data that is characteristic of epilepsy. Most importantly, it will require a new way of thinking about the evidence derived from big data in its application to health care and research. The greatest chances of success will lie in large national and international multicenter collaborations.

Statement of ethical publication.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.'

Disclaimer.

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Figure 1. Big Data “4Vs” of volume, variety, velocity and veracity as they apply to the epilepsy domain (Lhatoo 2017).

Figure 2: A screenshot of the Epilepsy Syndrome Seizure Ontology (ESSO) showing organization of terms to which testing (EEG, imaging, genetic testing) factors can be added.

Figure 3: A screenshot of the Epilepsy and Seizure Ontology (EpSO) showing the detailed class hierarchy of lateralizing signs associated with seizures and the use of class-level restrictions to model information at a fine-level of granularity, such as "left sign of 4" is related to left extended arm and it is a sub category of "sign of four".

Table 1 Large multicenter EEG databases

Database name	EPILEPSIAE	IEEG
Funding	EU	NIH
Year data provided	2013	2016 / ongoing
# data providers	3	>100
# data sets	275	>1000
Content	Scalp and intracranial long-term EEG recordings in epilepsy patients	Intracranial EEG recordings in epilepsy patients and animals
Raw data	Interictal + ictal EEG, 3D MRI	Interictal + ictal EEG, imaging
Metadata	Clinical information	Clinical information
EEG annotations	By human experts	By automated routines

TABLE 2. Population based sources of big data.

Data source	Sources	Advantages	Disadvantages
Administrative health records (AHR)	• National claims data • Regional claims data	• Often large and population-based • Longitudinal • No selection or recall bias • Cost-effective	• Not collected for clinical purposes • Different methods of coding • Lack granularity Lack of AHR phenotypes
Electronic Health Records (EHR)	• Clinical Practice Research Datalink (CPRD) • The Health Improvement Network database	• Often large and frequently population-based • Longitudinal • Coded by physicians for clinical purposes • More granular outcome data	• Different methods of coding • Different proprietary EHR software • Patients may move • Lack of EHR phenotypes
Health Survey Data	• Canadian Community Health Survey • US National Health Interview Survey • WHO World Health Survey	• Population-based • Standardized data collection • Patient reported outcomes • Comparability across populations of interest	• Self report may limit diagnostic accuracy • Response rates may vary • Often cross-sectional • Resource intensive
Vital Statistics Data	• Statistics Canada • United Kingdom Office of National Statistics • US National Vital Statistics System	• Population-based • Longitudinal data • Standardized data collection • Cause-specific death	• Inconsistent coding • Variable quality • Incomplete information • Delays in reporting