To the Editors:

We read with great interest the article by Hader et al. (2013), highlighting the safety of the most common surgical procedures performed for treating partial drug-resistant epilepsies. The authors report the results of a systematic review aimed at analyzing the morbidity in the context of epilepsy surgery, and conclude hoping “that these findings will increase the likelihood of appropriate referrals to specialized epilepsy centers for surgical evaluation.” In fact, the complication rate is generally low and the majority of adverse events are minor or temporary. This point can be strengthened not only considering the morbidity rate of epilepsy surgery itself, but also remembering that patients with drug-resistant epilepsy are at higher risk of sudden death and injuries, as well as psychosocial dysfunction and impaired quality of life (Kwan et al., 2011).

The literature search covers the period from 1990 to June 2008, looking for all studies in English that report seizure outcomes and complications from focal resective surgery and invasive electroencephalography (EEG) monitoring. Therefore, the authors report the complications that occurred during the implantation of depth electrodes and subdural grids and strips, positioned by means of burr hole, twist drill, or craniotomy.

Surprisingly, no studies reporting on stereo-EEG (SEEG) were included in the Systematic Review Results listed in Hader et al.’s (2013) Supporting Information. SEEG is a methodology developed by Talairach and Bancad at Hôpital Saint Anne, Paris, France (Bancad et al., 1965). Unlike depth electrodes (DE), the main goal of which is to lateralize the origin of the seizures, SEEG methodology aims to define the epileptogenic zone (EZ) by way of implanting a larger number of intracerebral electrodes according to a presurgical strategy based on the anatomo-electroclinical correlations (Munari et al., 1994). Some reports have clearly stated that, despite the number of electrodes, this result can be obtained with a very low complication rate (Cossu et al., 2005a,b; McGonigal et al., 2007). More recently, our group reported the results from a consecutive series of 500 SEEG procedures, with the last 81 (1,050 electrodes) performed according to an updated work flow (Cardinale et al., 2013). Only one status epilepticus and four minor complications occurred with the new method, which is based on three-dimensional image-guided robotic stereotactic implantation of the electrodes. Therefore, the major and minor complication rates per electrode were 0.1% and 0.4%, respectively. From an effectiveness perspective, 56% of the patients who underwent focal resections are free of disabling seizures with a minimum follow-up of 12 months. Gonzalez-Martinez and Bingaman reported in 2012 that “SEEG may be considered a rediscovered methodology that differs in principle from any other current method for extra-operative long-term monitoring used in the diagnosis and treatment of refractory focal epilepsy.”

In conclusion, we would like to highlight the historical rule and the future perspectives of SEEG, a methodology aimed at defining the EZ that is spreading beyond the European boundaries because it enables safe and effective recordings from every cerebral structure.

Disclosure

Dr. Cardinale reports receiving consulting fees from Renishaw-Mayfield and from Medtronic Italia. The Authors confirm that they have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Francesco Cardinale
francesco.cardinale@ospedaleniguarda.it

Giorgio Lo Russo
“Claudio Munari” Center for Epilepsy and Parkinson Surgery, Niguarda “Ca’ Granda” Hospital, Milan, Italy

References


The curse of in silico transformation from Palmini’s into the ILAE classification system of focal cortical dysplasia: A critical comment

To the Editors:

In their article, Fauser et al. (2013) could detect neither clinical nor outcome differences when comparing patients with temporal lobe epilepsy (TLE) with patients with focal cortical dysplasia alone (FCD International League Against Epilepsy [ILAE] type I) or when associated with hippocampal sclerosis (HS; FCD ILAE type IIIa). One hundred patients with TLE and “histopathology” diagnosis of “focal cortical dysplasia” were retrieved from their hospital files. Histopathology diagnosis of FCD was classified originally according to Palmini et al. (2004) and transformed into the 2011 ILAE system (Blumcke et al., 2011). As an example, Palmini’s FCD type 1a (20 cases) and type 1b (61 cases) were reclassified in silico and sine microscopium as ILAE type I (n = 31, with no imaging and/or histopathology evidence for HS), or ILAE type IIIa (n = 50, with imaging and/or histopathology evidence for HS). Only histories of febrile seizures were significantly more common in patients with ILAE FCD type IIIa compared to the cohort presenting with isolated ILAE FCD type I. Other clinical features did not allow any distinction between both FCD subtypes. Postsurgical seizure control was also not different between ILAE FCD type I versus type IIIa. Kaplan-Meier curves demonstrated >60% seizure control at 1-year follow-up and <50% long-term seizure freedom for both entities. In addition, they included a series of patients with FCD type II in their analysis. Microscopic parameters were identical between Palmini and ILAE classification systems for this diagnostic entity, and can be safely transformed. However, their analysis failed to statistically show significant long-term outcome differences compared to FCD types I and IIIa. These findings are interesting and partially also contradict previous results (Tassi et al., 2012), which urgently require more studies assessing the clinicopathologic relationship and predictive value of specific disease entities. However, such studies need also careful consideration of methodologic limitations to allow unambiguous interpretation of results. With this commentary, we would like to discuss the methodologic limitation of Fauser’s study in transforming histopathologic disease classification systems from one into another without careful microscopical reevaluation (i.e., in silico or sine microscopium). Although this approach may be used already in some other epilepsy centers, it is not appropriate for research purposes. It is our expectation that future work and study design will benefit from the discussion stimulated by this commentary.

Palmini’s classification system has been widely accepted in the international epileptology community. It was revisited by an ILAE Task Force in 2011, for the reason that some histopathology definitions of FCD subtypes were not proven reliable. As a prominent example, in an agreement study among nine North American neuropathologists, least agreement was achieved when judging Palmini FCD type Ib, reflecting the challenge to properly distinguish this subtype from normal cortical tissue (Chamberlain et al., 2009). It was the consensus of the ILAE Task Force to propose a classification system relying on careful histopathologic evaluation, giving at hand a microscopic description of histology features to better distinguish FCD subtypes. The ILAE classification system has been validated by a panel of 30 international neuropathologists with different access levels to epilepsy surgery material and achieved good interobserver and intraobserver agreement in the evaluation of the new FCD classification (Coras et al., 2012).

In Fauser’s work, the majority of patients with TLE presented with Palmini type Ib, which were subsumed as ILAE type I when imaging (or histopathology) excluded the presence of hippocampal sclerosis. No further subclassification into FCD ILAE type Ia, Ib, or Ic was made, thus there was a failure to specify patterns of aberrant radial architecture (FCD type Ia), tangential architecture (FCD type Ib), or a combination of both histopathology patterns (FCD type Ic). Indeed, the ILAE classification requires such specific histopathologic criteria for the diagnosis of FCD subtypes, and this should be always accomplished for research purposes to allow reliable comparison of data from different epilepsy centers by using the same terminology and thereby most probably describing similar patient series (Blumcke & Spreafico, 2011). Instead, Palmini’s FCD type has a vague definition as “architectural abnormality with giant or immature, but not dysmorphic neurons.” Such abnormalities can be also seen in other pathologic conditions and not always associated with FCD or any other epileptogenic brain lesion.

FCD associated with other principal brain lesions, that is, hippocampal sclerosis (FCD ILAE type IIIa), is specifically defined by the ILAE classification system and should refer to an architectural abnormality of supragranular layers 2
and 3, previously described as temporal lobe sclerosis in 10% of TLE patients with HS (Thom et al., 2009). Thom et al. also raised the discussion about this peculiar neuronal cell loss patterns representing an associated degenerative rather than independent dysplastic nature. This controversy remains to be clarified, as Tassi et al. (2010) did not observe any clinically significant differences when comparing TLE-HS patients with FCD or without FCD.

In conclusion, faint cellular abnormalities such as hypertrophic neurons in the cortical ribbon should be weighed with great caution and not regarded as unique or unmistakable criteria for FCD type I or III. Proper evaluation requires microscopic review of surgical specimens when used for scientific analysis of FCD or TLE patient cohorts. In silico transformation of Palmini’s FCD subtypes into the ILAE classification scheme is not justified, with the exception of FCD type IIa or IIb, as the ILAE classification defines and requires more refined histopathologic criteria. Therefore, Fauser’s data probably tells us that a patient series with humble histopathologic emphasis and expertise will not be helpful to better characterize the broad clinicopathologic spectrum of FCD.

**Disclosure**

The authors have no conflict of interest to declare. 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.

Ingmar Blümcke
bluemcke@uk-erlangen.de
Roland Coras
Department of Neuropathology, University Hospital Erlangen, Erlangen, Germany

**References**


**Commentaries**

The Editors invited the following commentaries on the article “Epilepsy informations and an ontology-driven infrastructure for large database research and patient care in epilepsy” (Sahoo et al., pp 1335–1341).

**Commentary on “Epilepsy informations and an ontology-driven infrastructure for large database research and patient care in epilepsy”**

When I was in training, a senior neurologist passed on an aphorism that he had been taught when he himself was a junior: “You don’t understand neurology until you understand epilepsy, and you don’t understand epilepsy until you have reclassified it.” I am not sure where this quip originated, but it makes an important point: epilepsy is difficult. The difficulty in understanding epilepsy reflects the extraordinary complexity of the human brain. As a result of this complexity, there are many different types of seizures and many reasons that people develop epilepsy.

In their recent report, the International League Against Epilepsy (ILAE) commission on classification and terminology repeatedly emphasize how limited our current understanding of epilepsy is, and the subsequent difficulties in developing a comprehensive classification (Berg et al., 2010). They suggest that their own proposals regarding classification should be seen as work in progress; they acknowledge that the classification system they proposed is not a definitive one, and will certainly change as our understanding of pathogenesis of seizures improves.

In their article, Sahoo et al. discuss some of the issues raised by the ILAE commission (Sahoo et al., 2013). Many
GRAY MATTERS

of these relate to the fundamental complexities of epilepsy and our inadequate understanding of the causes. In addition, epilepsy involves a diverse stakeholder community. Sahoo et al. emphasize that all people who use particular terms should mean the same things by them. They discuss problems that result from both semantic heterogeneity (when identical terms are used to describe heterogeneous information) and syntactic heterogeneity (differences in the format of data representation).

These are issues that have also been taxing those of working on the EpiNet project (Bergin et al., 2012). The EpiNet project was established to facilitate investigator-initiated clinical research in epilepsy. It has been designed to conduct multicenter cohort studies and to run simple pragmatic clinical trials. How do we ensure that all those who enter patients into the EpiNet database actually mean the same thing when they use specific terms? Does an epileptologist in one country necessarily interpret terms in the same way as a neurologist in a different country, or a different continent?

Clearly, these are important issues for a project such as EpiNet, which welcomes participation from a wide range of neurologists and epileptologists. If we cannot be sure that people mean the same thing by specific terms, then people will not have any confidence in the results that are produced. It is critical that the “garbage in, garbage out” scenario is prevented.

EpiNet will address some of these issues by undertaking a series of validation studies. However, it would certainly be of major benefit to us—and presumably others involved in research—if there was widespread acceptance of meanings for specific terms, and how different conditions relate to one another.

Sahoo et al. propose a solution to many of these issues. They suggest that the epilepsy community undertakes a formal classification process using “informatics.” Their proposal is that the epilepsy community develops an “ontology.” The ontology should incorporate well-defined semantics that allow precise definition. The ontology would comprise a “formal representation of knowledge in the domain of epilepsy that allows both human users and machines to consistently and accurately interpret terms.” Epilepsy terms would be classified along a number of distinct dimensions according to specific application requirements. Named relationships would be used to describe the various subcomponents of structures, as well as functional relationships. Sahoo et al. point out that introducing an ontology would have multiple benefits, including improving clinical decision support, access to information for patients and their families, data sharing, and secondary use of clinical data. Another benefit would be that an epilepsy ontology would be able to interact with other ontologies outside of epilepsy. Sahoo et al. state that the integrated terminology system associated with the epilepsy ontology will make software applications more reliable, because the ontology allows accurate interpretation of the terms. However, to do this, Sahoo et al. assert that it is important to “move beyond a document-based encoding to use of a formal knowledge representation language that can be directly integrated into informatics tools.” They discuss other problems involved in creating an ontology, and make the particular comment that “ontology languages have not so far had a straightforward mechanism to address the issue of dynamic classification of terms.”

As someone involved with clinical research, I was very interested by the proposal of Sahoo et al., since it addresses several of the issues with which we at the EpiNet project have struggled. I had relatively little difficulty understanding the broad concepts. However, I did have difficulty with some of the detail. The authors use terms that are presumably familiar to those working in the field of informatics, but which are not necessarily in common use by those working in the field of epilepsy; these include terms such as granularity, interoperability, and even informatics itself. They talk of “specialization-generalization relationships,” “two-dimensional matrix,” and “formal knowledge representation language,” although the terms are not well defined.

In the longer term, the detail will be important, but at this stage I think Sahoo et al. are seeking agreement on general principles. To this end, I agree that the goal is certainly one worth striving for. If the epilepsy community can successfully create an ontology that is universally accepted, then it will be a major advance, particularly with regard to research, but also in terms of management of individual patients. However, it will not be easy. I fear that Sahoo et al. may have underestimated the difficulty in producing the epilepsy ontology. I genuinely hope that the epilepsy community can reach a consensus in this area, but Sahoo et al. themselves noted the controversy that has followed the attempt by the commission on classification and terminology to move in this area. Notwithstanding these concerns, I think the proposal to create an epilepsy ontology is an excellent one, and I remain cautiously optimistic that it will eventually be successful. I am encouraged to learn that there has been widespread acceptance of the ontologies created in the fields of genetics and oncology. Those of us working on the EpiNet project would be happy to participate in the development of an epilepsy ontology.

Disclosure

I have no conflicts of interest to disclose. I confirm that I have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Peter Bergin
pbergin@adhb.govt.nz
Department of Neurology, Auckland City Hospital, Auckland, New Zealand

Epilepsy, 54(8):1505–1511, 2013
The review in this issue by Sahoo et al. (2013) recommends that modern informatics techniques in the form of an “ontology” can serve as a means of assisting the current dilemmas regarding epilepsy classification. What is an “ontology,” how does it differ from a “classification,” and what are the perceived advantages?

The common understanding of a “classification” such as we use for seizures and epilepsies is a hierarchical structure about a particular domain of knowledge. Other words that enter into the discussion of organizational schemes include terminologies, taxonomies, and controlled vocabularies. The definitions and implementations of each vary somewhat with the domain being considered and the application for which it is intended. In the realm of biology, we are most familiar with the taxonomy used to describe animal life (i.e., kingdom, phylum, class, order, family, genus, species) based on the principle of who can reproduce with whom. Similarly, the classification of the seizures as described by the International League Against Epilepsy (ILAE) Commission on Classification and Terminology (CTC) in 1981 has as an organizing principle, partial versus generalized ictal onset. Both classifications have great appeal owing to the clarity of the organizational principle, resulting structure, and utility for teaching the topic (domain) being considered. However, what if we wish to consider other aspects of animals such as location, color, feeding behavior, modes of movement, required nutrition, genome, and so on? The complexity of knowledge regarding animals is simply too great to be captured by a taxonomy with only one major axis for distinguishing the members to be considered. Although knowledge about seizures and epilepsies is much more restricted than that of all animals, the concept of complexity pertains. The multiple types of knowledge that are pertinent in this domain defy a simple one or two (or three or four) tiered classification system. The need for a “multidimensional” system was recognized prior to the most recent ILAE CTC Task Force recommendations (Berg et al., 2010) in a 2001 revision (Engel, 2001) that suggested a five-axis diagnostic scheme to characterize seizures and epilepsies. That suggested revision also failed to gain traction in the epilepsy community. Therefore, it would be useful to conduct a “root-cause” analysis of why we have failed to come to consensus despite many hours of work by highly competent individuals with only the best of intentions and potential solutions. How do we move past the current intellectual “gridlock”?

**GRAY MATTERS**

**REFERENCES**


**Informatics—a computational approach to the complexity of the epilepsies**

The first is the need to acknowledge the complexity of knowledge that exists about seizures and epilepsies as well as the multiple uses of that knowledge. These are interrelated concepts. So much of the discussion appropriately focuses on what is needed to provide optimal care for those with seizures. In this context, the information provided by knowledge about seizure onset (focal vs. generalized), with or without impairment of consciousness, and likely etiologies are extremely important. By extension, these “descriptors” are necessary for the development of new therapies based on current strategies. However, the reality exists that this level of knowledge may not be available in resource-challenged regions of the world, in which some degree of diagnosis and management must occur. At the other extreme of clinical care, more precise information is required to perform epilepsy surgery or design new biologic agents based on causative genetic mutations. As soon as we desire to incorporate clinical science (necessary to establish the relationships between individual concepts) and basic science (necessary to understand the mechanisms resulting in seizures), it becomes clear that a relatively simplistic classification system is not up to the task for all stakeholders.

**Recognition of Complexity**

**Available Solutions**

All that is required to deal with this challenge is community acknowledgement of the complexity of seizures and epilepsies, along with a willingness to accept the reality that different “subclassifications” will be needed to address individual applications and contexts in which the knowledge is required. However, these must be harmonized so that one piece of knowledge means the same in each “subclassification.” The ILAE should play a major role in this effort as the internationally recognized organization in this domain.

**Common Definitions**

The second is the need to arrive at common definitions for core terms and concepts. Any attempt to provide an internally consistent system of knowledge with application
across the multiple dimensions required for a complete characterization of seizures and epilepsies will be thwarted unless this can be achieved. Of note, this pertains whether the knowledge is discussed by people or computed by machines. “Idiopathic” cannot mean “unknown” and “of presumed genetic etiology,” as these are not synonymous. The situation becomes even more precarious if other modifiers are assumed without clear limits such as pharmacoresponsiveness, age of onset, and spontaneous remission. The same situation applies to the more complicated concept of an “epilepsy syndrome.” Definitions must exist for there to be clarity across users.

**Available Solutions**

A great deal of literature has already been developed to address this need. The National Institute of Neurological Disorders and Stroke (NINDS) has published common data elements for seizures and epilepsies (Loring et al., 2011). Highly regarded glossaries exist for seizures and epilepsies ILAE (Blume et al., 2001) and EEG (Noachter et al. 1999). The rate-limiting step in achieving consistency is illustrated in Fig. 2 of the review by Sahoo et al. (2011). The manner in which each of these characterizations of seizures and epilepsies will be thwarted unless this can be achieved. Of note, this pertains whether the knowledge is discussed by people or computed by machines. “Idiopathic” cannot mean “unknown” and “of presumed genetic etiology,” as these are not synonymous. The situation becomes even more precarious if other modifiers are assumed without clear limits such as pharmacoresponsiveness, age of onset, and spontaneous remission. The same situation applies to the more complicated concept of an “epilepsy syndrome.” Definitions must exist for there to be clarity across users.

**An Adequate Framework**

The third is a framework in which this knowledge needs to be “assembled” in a manner that allows use by multiple stakeholders. As described earlier, a tiered system organized around a few defining features is not adequate to achieve this goal. The text document that we have been using for decades (handwritten or electronic) does not have the intrinsic capacity to enable organization. Putting information into a database format (such as those that are on the backend of electronic health records) allows sorting and some re-use of data.

**Available Solutions**

This where the concept of an ontology as a framework of knowledge becomes crucial. Furthermore, there must be a “language” that provides the information that is incorporated into that framework. The nature of modern ontologies allows incorporation of concepts along multiple axes. The structure uses individual pieces of data that are then incorporated into larger concepts that are connected to each other (relationships) by rules based upon knowledge of the domain (e.g., staring + 4–10 years old + 3 Hz spike-wave EEG = Childhood Absence Epilepsy). The manner in which each of these demographic, symptoms, signs, and EEG dimensions can be reassembled into different concepts (syndromes) is illustrated in Fig. 2 of the review by Sahoo et al. (2013). The clinician or laboratory scientist need not be concerned with technology behind the ontology or the language in which it is written (e.g., OWL, Ontology Web Language) any more than we are knowledgeable about how any of the commonly used databases are constructed. These are simply new tools available for us to organize information so as to improve clinical care, teach, and serve as a basis for discovery.

There are additional advantages that flow from the development of a seizure-epilepsy ontology; these include the heuristic value of determining the experiments that needs to be obtained to create the rules that relate one concept to another; the ability to harmonize multiple classification systems (e.g., International League Against Epilepsy, Systematized Nomenclature of Medicine Clinical Terms, and the International Classification of Diseases coding). The latter is of particular importance as it serves as the basis for assessing disease burden, code driven research, and reimbursement in some countries.

How is this sea change to be implemented, as the necessary software and hardware are now readily available? The authors suggest a consortium approach. Ideally this should be informed by the ILAE as the international body that has traditionally guided the seizure and epilepsy classification process. Parallel with the creation of a consortium is the need to educate all stakeholders about the language of clinical informatics. Just as we needed to learn the terminology of molecular genetics a decade ago (allelic heterogeneity), so now we need to understand the basic concepts of clinical bioinformatics (semantic heterogeneity), which has some striking similarities to the language of molecular genetics. Perhaps the most significant challenge is for us as individuals to give a little autonomy with regard to preferred terms and concepts so as to reap the great potential advances that come with a unified framework for the domain of epilepsies facilitated by modern computational methodologies.

**Disclosure**

The author has no conflict of interest disclosures and confirms that he has read the Journal’s position on issues involved with ethical publication and affirms that this report is consistent with those guidelines.

Jeffrey Buchhalter
jeffrey.buchhalter@albertahealthservices.ca
Alberta Children’s Hospital, Calgary, Alberta, Canada

**References**


**ANNOUNCEMENTS**

**13th European Conference on Epilepsy & Society**

**5th CAAE International Epilepsy Forum**

**1st International Summer School for Neuropathology and Epilepsy Surgery**
September 16–20, 2013 in Erlangen, Germany. Applications (deadline June 3, 2013) to Prof. Ingmar Blüemcke at ingmar.bluemcke@uk-erlangen.de

**2nd International Symposium on Hypothalamic Hamartomas**

**5th Eilat International Education Course: Pharmacological treatment of epilepsy**

**6th European Society for Stereotaxic and Functional Neurosurgery Hands-On Course: Epilepsy Surgery**

**7th Migrating Course on Epilepsy**

**Indian Epilepsy School 2013**
November 13–16, 2013 in Delhi, India. Registration to indianepilepsysociety@gmail.com. [http://www.ilae.org/Visitors/Congress/congressinfo/IndianEpilepsySchool-2013.pdf](http://www.ilae.org/Visitors/Congress/congressinfo/IndianEpilepsySchool-2013.pdf)

**2013 American Epilepsy Society Annual Meeting**

**4th Course on Epilepsy Surgery (EPODES)**