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Review article

The new definition and classification of seizures and epilepsy

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ABSTRACT

This review discusses the updated classifications of seizures and the epilepsies, which were recently published by the International League Against Epilepsy (ILAE). While it is always a challenge to learn a new classification system, particularly one that has remained essentially unchanged for over three decades, these new classifications allow for the inclusion of some previously unclassifiable seizure types and utilize more intuitive terminology. In this review, we specifically discuss the use of these new classifications for patients, clinicians, and researchers.

1. Introduction

Classifications for seizures and epilepsy were previously constructed in 1981(ILAE, 1981), 1985 (ILAE, 1985) and 1989 (ILAE, 1989). Having seizure and epilepsy classifications are exceedingly important for the clinicians and care teams, patients and families, and researchers. From a patient standpoint, it provides a namable diagnosis/etiology and improves understanding. For clinicians and the patient's care team, these classifications enhance communication and discussion. From a research standpoint, having these classifications enables investigation of drug or surgical treatments, responses, and typical clinical courses for different types of seizures and epilepsy.

Based on decades of accumulated clinical experience, the International League Against Epilepsy (ILAE) commissioned a new operational classification of seizure types and epilepsies. The new 2017 classifications, when compared to the 1981/1985/1989 classifications, utilize alternative terms and contain several important additions. These changes improve the intuitiveness, transparency and versatility of the classifications, and allow for inclusion/classification of previously unclassifiable seizure and epilepsy types.

2. History of seizure and epilepsy classifications

Seizure classifications have existed for centuries, with the first modern classification proposed in 1964 (Gastaut et al., 1964), and international use of this classification popularized in 1970 (Gastaut, 1970). Prior to 1970, distinction between seizure types and epilepsy types was not frequently made. This distinction is important as a large percentage of patients with seizures are unclassifiable as to a specific epilepsy type according to the 1989 criteria (32% and 39% in two studies of 100 and 300 consecutive patients, respectively) (Seino, 2006). For these patients, their seizure type can and should still be classified, emphasizing the utility of having separate classifications.

The seizure classification was first updated in 1981, prompted by the widespread use of video electroencephalography (EEG), which had impacted clinical practice. The 1981 seizure classification promulgated the terms "simple partial", "complex partial", "generalized", and "unclassifiable" that have been in use until today (ILAE, 1981). At the beginning of the 21st century, the ILAE sought to update the seizure classification again. Extensive discussions resulted in a decision in 2010 to maintain the 1981 classification of seizures with minor changes (Berg and Scheffer, 2011; Engel, 2001, 2006). The classification of the epilepsies were partially updated in 1985/1989 (ILAE, 1985, 1989) and then again in 2010 (Berg et al., 2010; Berg and Scheffer, 2011), with the 2010 revision being an intermediate stage aiming towards a final accepted epilepsy classification.

While it has been clear for some time that updated classifications were needed, consensus was difficult to reach. This need prompted the ILAE to assemble a new task force, which developed and published a new definition of epilepsy in 2014 (Fisher et al., 2014), then final classification of seizures (Fisher et al., 2017a,b) and the epilepsies (Scheffer et al., 2017) in 2017. Interestingly, some of the alternative terminology adopted in the 2017 seizure classification (focal instead of partial, and the term "aware") were terms considered, debated, and contentious in 1981, and have continued to stir controversy (ILAE, 1985).

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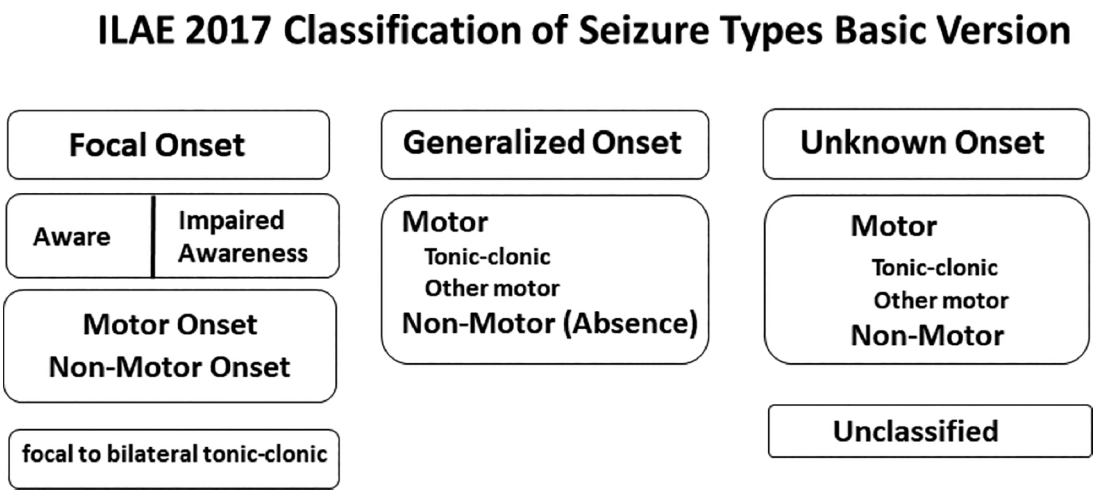

Fig. 1. ILAE 2017 classification of seizure types basic version.
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Given the advances in neuroimaging, genomic technologies and molecular biology, it was proposed to move towards a scientifically based classification of seizures, but after intense discussion it was felt this was not currently tenable. The new classification of seizures continues to rely on semiology, EEG and occasionally supplementary information from imaging. Classification of the epilepsy type and epilepsy syndrome does utilize more of these recent advances, being aided significantly by genetics, lab findings and neuroimaging findings, though still with a major focus throughout the diagnostic process on etiology.

3. Definition of seizure and epilepsy

An epileptic seizure is defined conceptually as: "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain." This definition was updated most recently by the ILAE in 2005 (Fisher et al., 2005) and was not changed in 2014 when the definition of epilepsy was updated (Fisher et al., 2014).

Epilepsy exists when someone has an epileptic seizure and their brain "demonstrates a pathologic and enduring tendency to have recurrent seizures" (Fisher et al., 2014). More specifically, epilepsy is diagnosed when an individual has: 1) at least two unprovoked or reflex seizures > 24 h apart, 2) one unprovoked or reflex seizure and a probability of having another seizure similar to the general recurrence risk after two unprovoked seizures (≥60%) over the next 10 years, or 3) an epilepsy syndrome (Fisher et al., 2014). Greater than 60% was chosen as this is the lower limit of the confidence interval for someone with two unprovoked seizures having another seizure (Hauser et al., 1982). Examples of evidence that increases the probability of having additional seizures include: 1) epileptiform activity on EEG or 2) a potential epileptogenic abnormality on brain imaging. A recent study (PRO-LONG) evaluated patients who were diagnosed with epilepsy according to this new definition (2014) *vs*. the old definition. PRO-LONG found the long-term recurrence of seizures in patients diagnosed with the new definition was 83.6% at 10 years, thus supporting treatment and a diagnosis of epilepsy after only one seizure (Beretta et al., 2017). Thus, if the clinical picture, EEG or imaging findings increase the probability of another seizure to ≥60%, then these individuals are defined as having epilepsy, and should be, as clinically they are statistically equivalent in their recurrence risk to those who have had two or more unprovoked seizures.

Epilepsy is considered "resolved" under the following circumstances: 1) in a patient with an age-dependent epilepsy syndrome who is older than the age in which this syndrome is active, or 2) a patient who has been seizure free for ≥10 years and has been off all anti-seizure medications for ≥5 years.

Epilepsy was redefined by the ILAE as a "disease" and not a "disorder" (Fisher et al., 2014). The term "disease" better emphasizes to patients, clinicians and society the importance and impact of epilepsy. Although some might worry that "disease" carries more stigma, important diseases such as cancer, diabetes, and heart disease, are all diseases, not disorders.

The definition of epilepsy, a diagnosis for an individual, and a decision about whether to treat, are linked, but diagnosis of epilepsy does not mandate treatment and not all epilepsy requires treatment. Treatment decisions must be individualized. The changes made in 2014, as outlined above, compared to the prior definition from 2005, align the definition and resolution of epilepsy with clinical practice.

4. Classification of seizure types

The new classification has both a basic and expanded version, depending upon the needs and expertise of the individual utilizing the classification. The basic version is a contracted form of the expanded version. The expectation is the basic version will be more useful for doctors in general practice, pediatricians, non-neurologists and general neurologists, nurses and health care workers, while the expanded version will aid epileptologists/neurophysiologists and researchers. Though, clearly there will be researchers who only want the information the basic classification contains, and others mentioned above may prefer the detail of the expanded classification. It should be noted that one should be reasonably sure an event is epileptic prior to attempting to classify a seizure and epilepsy type.

The classification applies to seizures in adults as well as children, except for neonatal seizures—for which there is a separate classification. This classification does not attempt to classify subclinical electrographic seizures (Fig. 1).

4.1. Basic classification

Seizures are defined by onset as: focal, generalized, unknown, or unclassifiable. "Focal" is synonymous with the old term "partial." The term "generalized" has been retained unchanged. A generalized onset seizure is when both hemispheres (potentially asymmetrically) are activated at onset of the seizure, according to behavior and EEG. "Unknown" onset refers to when the onset is unknown but other manifestations are known. This is clarified further below. "Unclassified" remains as a category, although usage may decrease given the addition of additional seizure types and the "unknown onset" category. Few events are clearly seizures, yet unclassifiable (Fig. 2).

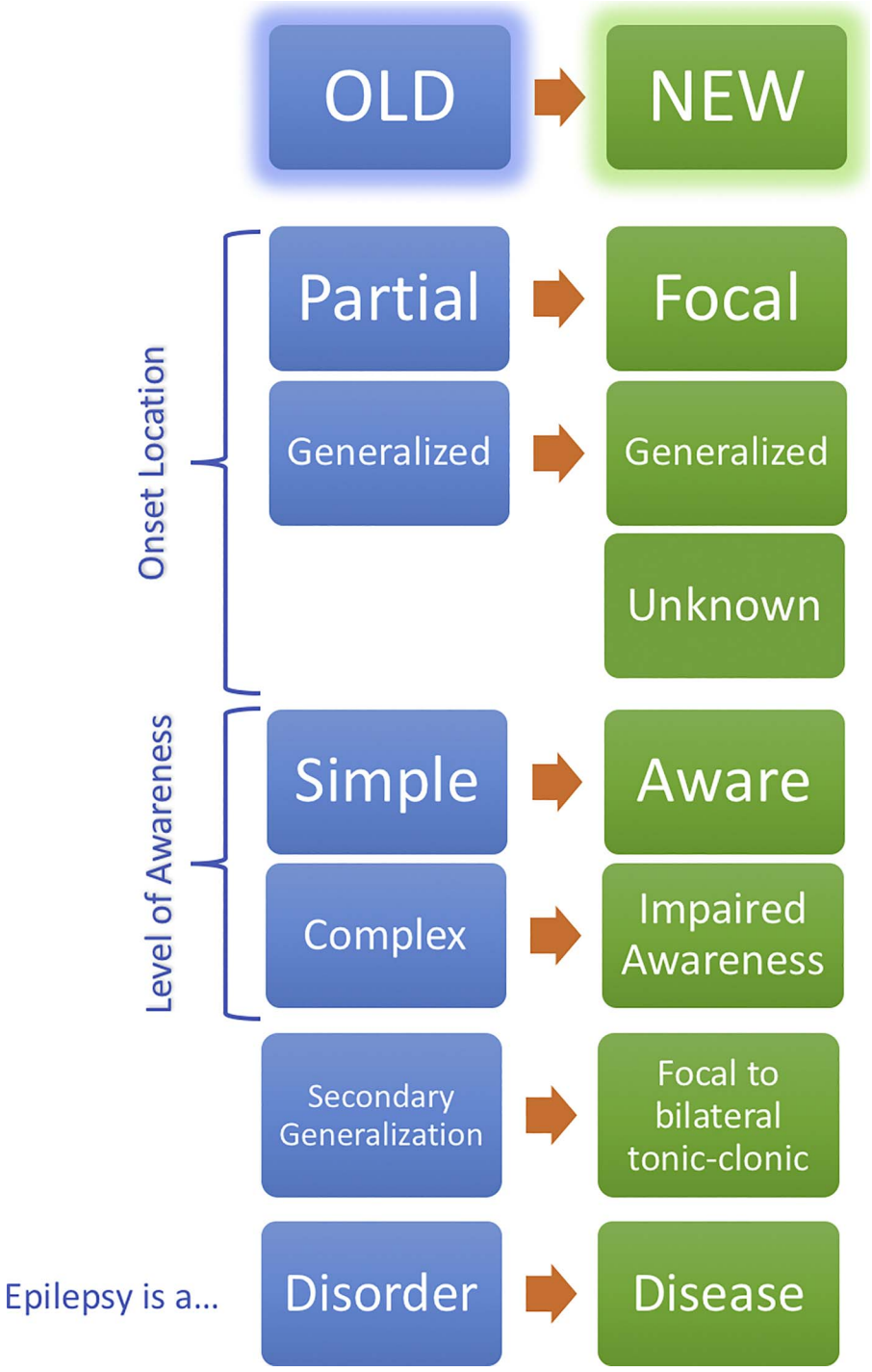

Fig. 2. Mapping of prior 1981 terminology to the new 2017 terminology.

Focal seizures optionally are classified as "aware" or "impaired awareness" seizures. These terms map to the former terms "simple" and "complex," respectively. Impaired awareness and loss of consciousness are not synonymous. If awareness in impaired at any time during a focal seizure, "impaired awareness" should be included. This is an exception to the "rule of first," where the first sign or symptom defines the seizure type, even if more prominent features occur later. If awareness is unknown, then this level of classification should be omitted when classifying the seizure type. In the basic classification, the next step after consideration of the level of awareness for a focal seizure entails defining the onset as "motor" or "non-motor." The expanded classification includes subdivisions with more granularity. Secondarily generalized seizures are now called "focal to bilateral tonic-clonic seizures," in order to restrict "generalized" to seizures of generalized onset.

When classifying generalized seizures, "aware" *vs.* "impaired awareness" is omitted, since awareness is impaired in most generalized seizures. The "motor" or "non-motor (absence)" designation is used as well. Generalized motor seizures can further be classified as "tonic-clonic" or "other motor." Unknown onset seizures can also be classified as "tonic-clonic" or "other motor."

Any name can omit unambiguous words, such as focal tonic, instead of focal motor tonic. Caution is advised in the use of "tonic-clonic," as this term has a specific definition and should not be used as a waste-basket term for all motor activity. The word "onset" can also be omitted where its meaning is implied.

The nature of seizure onset is crucial, and a seizure whose onset was

unwitnessed, followed by tonic-clonic activity should be labeled an "unknown onset to bilateral tonic-clonic seizure." The level of confidence for declaring a focal or generalized onset is somewhat arbitrarily set to 80% confidence (paralleling the usual permissible false negative rate in clinical statistics).

4.2. Expanded classification

The expanded classification builds on the basic classification described above, expanding the "motor" and "non-motor" categories under all three types of seizure-onsets (focal, generalized, and unknown).

A focal motor seizure is classified by first determining whether awareness is impaired during any part of the seizure, thereby rendering it a *focal impaired awareness seizure*. In cases where awareness is unknown or cannot be assessed (for example, during a brief focal atonic seizure), mention of awareness can be omitted.

The next level of classifier derives from the first sign or symptom of the seizure, even if not the ultimately most prominent sign or symptom. The first symptom marks the seizure focus or network. An exception is a *focal behavior arrest seizure*, which must show behavior arrest as the predominant sign during the entire seizure, since brief behavior arrest is hard to determine. These further classifiers (ex. automatisms, emotional) are listed in Fig. 3.

After seizure classification, addition terms are welcome, either from the seizure classification, a suggested list of seizure descriptors (Fisher et al., 2017b), or free text. To illustrate, a seizure could be characterized as a *focal impaired awareness autonomic seizure* with left face numbness and anxiety. Only the words here in italics would be the seizure type.

5. Classification of epilepsies

The ILAE position paper by Scheffer and colleagues describes a new classification of the epilepsies, which now incorporates a major focus on etiology at each step of the diagnostic process (Scheffer et al., 2017). The Epilepsy classification applies to all ages.

After classification of seizure type, the clinician should aim to identify the patient's epilepsy type and where possible, their epilepsy syndrome. Patients who do not meet criteria for epilepsy (ex. single seizure) should be classified as to a seizure type but classification should stop there. To classify an epilepsy type a patient must have met the definition of epilepsy, as defined in 2014 (Fisher et al., 2014). Additionally, even if criteria for epilepsy is met, there will be patients whose seizure type is classifiable, but their epilepsy type is unclassifiable.

The epilepsy type classification is broader in scope than is the seizure classification, and considers the possibility of having multiple seizure types, and incorporates information about the overall clinical picture, imaging, genetics, laboratory tests, prognoses and comorbidities. In many instances, the syndrome and etiology provide additional information that is critical in guiding the patient's management.

Epilepsy types are classified as: 1) Focal 2) Generalized 3) Combined Generalized and Focal 4) Unknown. To place a patient into one of these categories one uses the classification of all types of seizures that a patient has, and then maps those in aggregate to one of these four categories. The new group of "Combined Generalized and Focal Epilepsy" has been devised in recognition that there are epilepsy syndromes, such as Dravet syndrome and Lennox-Gastaut syndrome, in which it is usual to have both generalized and focal seizures. An epilepsy type is a separate designation than an epilepsy syndrome, and the two should not be confused.

Epilepsy syndromes refer to clusters of features (seizure type(s),

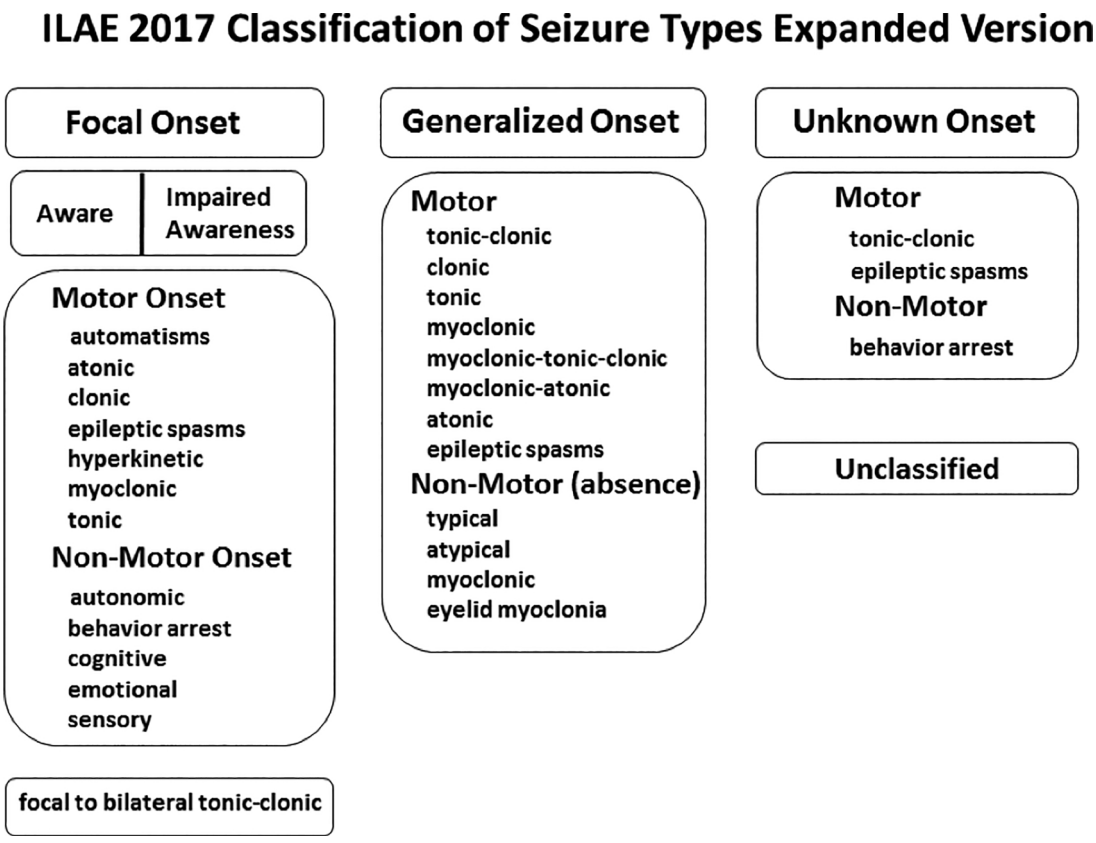

Fig. 3. ILAE 2017 classification of seizure types expanded version.
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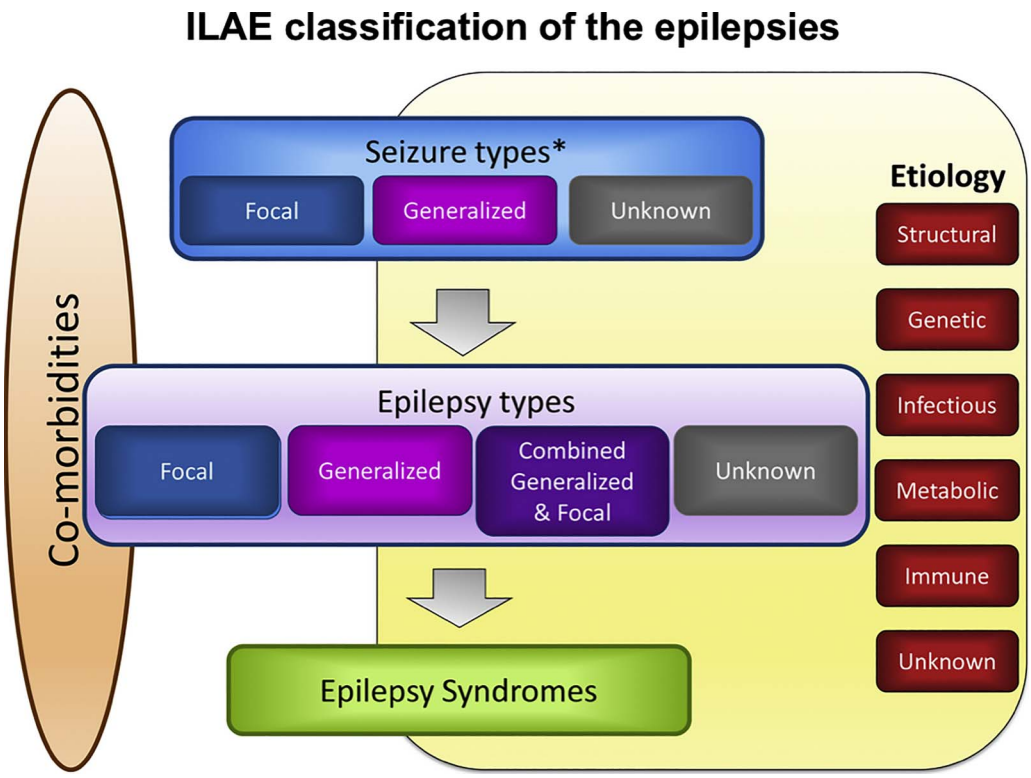

Fig. 4. ILAE 2017 classification of the epilepsies.
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EEG findings, imaging findings, age-dependent features, triggers and sometimes prognosis) that occur together. Many of these have well-recognized names. An epilepsy syndrome diagnosis provides more sophisticated information than does an epilepsy type diagnosis for some patients. While there are many well recognized syndromes, the ILAE has never formally classified a list of epilepsy syndromes (Berg et al., 2010; Scheffer et al., 2017). New syndromes are constantly emerging and further classification of epilepsy syndromes is likely to be a focus of future ILAE endeavors (Fig. 4).

6. Epilepsy etiology

From first contact with a patient, the clinician is encouraged to consider the etiology of their seizures. If not clear at initial presentation, the etiology should be reconsidered at all further decision points, given its critical impact on epilepsy management and prognostic counseling. The ILAE Task Force has defined six etiologic categories, focusing on those etiologies with management implications. These categories are: 1. structural; 2. genetic; 3. infectious; 4. metabolic; 5. immune; and 6. unknown. These are not hierarchical and more than one might often apply. Further clarification and description of what would fall into these etiologies is as follows:

1) Structural etiology: a finding on neuroimaging reasonably inferred to cause the patient's seizures due to concordant EEG and clinical findings (Lapalme-Remis and Cascino, 2016). An imaging abnormality with discordant seizure semiology and EEG findings is likely unrelated to the patient's epilepsy and would not be considered relevant when determining their epilepsy type (Scheffer et al., 2017).
2) Genetic etiology: a specific disease-causing variant in a gene or copy number variant, believed to be pathogenic for epilepsy, would lead to a genetic classification. Having a relevant family history and typical features (EEG, seizure semiology) without the molecular genetics is sufficient for a genetic etiology classification. Determining when a genetic variant is causative remains challenging, with many patients having variants of unknown significance. Genetic disease-causing variants often arise *de novo* and are not inherited, so a family history of epilepsy is frequently not present, despite the patient having a genetic cause for their epilepsy (Hildebrand et al., 2013).
3) Infectious etiology: refers to a patient with epilepsy, not a patient with seizures due to an acute infection. A patient with an acute infection and seizures does not have epilepsy as their seizures are provoked (and thus no epilepsy type classification should be made). Infectious etiologies are exemplified by: neurocysticercosis, HIV, CMV, cerebral toxoplasmosis, many of which could also be considered a structural etiology. Classifying these cases as infectious has treatment implications and thus would often take precedence over a structural classification. But, whichever is more relevant to the management issue can be prioritized as the etiological category. Patients with seizures due to a resolved infection (*e.g.* meningitis) would be classified as having an infectious cause of their epilepsy (Vezzani et al., 2016).
4) Metabolic epilepsies: refers to a patient with epilepsy in which the core of the epilepsy is due to a metabolic derangement. Someone with a transient metabolic disturbance resulting in acute-symptomatic seizures would not qualify as their seizures are provoked, and therefore they do not have epilepsy. Many of the metabolic epilepsies are genetic in etiology, but some may be acquired. Examples include pyridoxine-dependent seizures and cerebral folate deficiency (Parikh et al., 2015).
5) Immune etiology: when an auto-immune disease is the cause of new-onset epilepsy. Antibody mediated limbic encephalitis is an increasingly recognized cause of seizures in epilepsy of unknown origin, though it should be noted that this etiology does not exclusively refer to limbic or extra-limbic encephalitis. Autoimmune encephalitis and epilepsy have been linked to both neuronal intracellular antibodies (GAD65, ANNA-1, and Ma) and neuronal cell surface antibodies (VGKC complex, NMDAR, AMPA, GABA-B, and GluR5). (Correll, 2013; Toledrano and Pittock, 2015).
6) Unknown category, for patients whose etiology remains unclear.

For patients with two or even three etiological categories, all etiological categories can be recognized. In specific instances, whichever is more relevant to the question being asked should be applied. The above descriptions are a brief summary, and it is suggested to refer to the paper by Scheffer et al. for more detailed explanations (Scheffer et al., 2017).

7. Rationale for changes to the classification

Reclassification and renaming are effortful, but can be worthwhile if the new classification is more intuitive and transparent for patients, non-clinicians and clinicians, enables classification of formerly unclassifiable seizure types, and provides a more practical structure for the classification of epilepsy types. Time and experience will indicate whether the ILAE revisions meet these goals.

7.1. Changes that will assist neurologists, other clinicians, and patients

The word “partial” was chosen in 1981, as it was felt “focal” was suboptimal to describe seizures that could involve large parts of a hemisphere. The current classification has chosen “focal,” given that this term is more widely understood. The terms “simple” and “complex” for degree of awareness were not intuitive for clinicians or patients and were commonly misunderstood. The old terminology caused some patients to think that “simple” seizures were not a big problem, while “complex” seizures were complicated – neither of which was a true inference. Changing “secondarily generalized tonic-clonic seizure” to “focal to bilateral tonic-clonic” was done to reserve “generalized” for generalized onset seizures only. “Bilateral” was added to indicate propagated seizures.

The additional terms that can and should be appended in the extended classification (*e.g.* cognitive, automatisms, *etc.*) will provide patients with a more specific description (sometimes improving diagnosis), which is frequently desired by the patient and aids them in better understanding their disease. Some seizure types were completely omitted in the old classification. Telling a patient that they had epilepsy but being unable to give them a subtype of their seizures can confuse patients. Nevertheless, not every seizure type can be included in a classification.

7.2. Changes that will assist research

The new classification provides flexibility in providing as much information as possible using specific terms within the categories. Additional terms in the expanded seizure classification will help to categorize seizures with similar semiology. These additional terms will enable researchers to utilize them for targeted drug therapy, correlations with genetics, or important features of seizures. Use of more specific terms will enable clinicians and researchers to better communicate about more specific groups of patients with epilepsy. We hope that inter-rater reliability will be high, but this is to be determined and will have to be evaluated when the classification has been in use for a period of time. Kang et al. evaluated inter-rater reliability for diagnosis and classification of epilepsy from medical chart review using the old definitions and found high inter-rater reliability (Kang et al., 2013).

When designing future studies one could chose to design them similarly to the past as the same information that was previously available will still be available if one only cares about difference between generalized and focal seizure types, for example. Alternatively, or one could design studies with more granularity to evaluate just a specific subgroup (ex. patients with focal autonomic seizures).

The new seizure classification allows clinicians to provide some information when the nature of the onset (focal or generalized) is unknown, enabling some seizure types to be removed from the black box of “unclassifiable.” It also provides a place to classify seizure types that can have either a focal or generalized onset (*e.g.* epileptic spasms) but for which the onset may be unknown in a particular case. Why there are so many different types of seizures is unclear, and should be motivation for the research community to clarify the underlying pathophysiology.

8. Conclusion

These new classifications will provide a framework to improve our understanding of seizure and epilepsy diagnoses for patients, clinicians, and researchers. While significant debate led to the consensus that resulted in the updated operational classifications, it will take the adoption and regular use of these new classifications by clinicians and epileptologists to produce the potential benefits described above.

Conflict of interest

Jessica Falco-Walter has no financial interest or conflict of interest to declare. Ingrid Scheffer and Robert Fisher have no conflicts relevant to definition or classification of epilepsy. Robert Fisher has stock options in Avails Medical (testing of substance levels), Zeto (dry EEG), Cerebral Therapeutics (infusion of drugs into CSF), Smart Monitor (shake/seizure detector) and he consults for Engage Therapeutics. Ingrid Scheffer has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline and Nutricia; editorial boards of the *Annals of Neurology, Neurology* and *Epileptic Disorders*; may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has received speaker honoraria from GlaxoSmithKline, Athena Diagnostics, UCB, Eisai and Transgenomics; has received funding for travel from Athena Diagnostics, UCB, Biocodex, GlaxoSmithKline, and Eisai; and receives/has received research support from the National Health and Medical Research Council of Australia, National Institutes of Health, Australian Research Council, Health Research Council of New Zealand, CURE, American Epilepsy Society, US Department of Defense Autism Spectrum Disorder Research Program, March of Dimes, and Perpetual Charitable Trustees.

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