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Article type : Commentary

TITLE: The 2017 ILAE Classifications of Seizures and Epilepsy are steps in the right direction

(Response to Lüders et al. 2019, Critique of the 2017 Seizure Type and Epilepsy Classification)

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/EPI.15052

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Key words: seizure, epilepsy, classification, focal, generalized

The main purposes of the 2017 ILAE operational classification of seizures [1; 2] and the epilepsies [3] are to provide a common language to aid clinicians in diagnosis and management of individual patients and to be of value for research and scientific study. The ILAE classification advances a system suitable for use by a wide range of medical professionals, without need for expensive technology. The revised classification is an evolutionary advance from the previous classification, thereby avoiding unnecessary disruption. Lüders and colleagues suggest that a seizure classification should be based on semiology, a concept that he and his students have promulgated for decades [4]. However, little evidence exists that a more complex scheme that places greater reliance on semiology would serve the broad needs of the epilepsy community. The argument is made that the ILAE 2017 classifications comprise several inadequacies. Their major criticisms will be addressed individually.

Universal acceptance: Lüders and associates argue that "A classification system should ideally be universally accepted." Nothing is universally accepted. For a useful classification, acceptance grows over time and usage.

Semiology: Mixing semiological and electro-anatomical data (but very much emphasizing semiology) was an intentional choice of the developers of the ILAE 2017 classification. In this operational classification, we thought it best to use all available information to classify a seizure. Imagine a seizure with behavior arrest and staring. This could either be an absence or a focal impaired awareness seizure, but an EEG often makes the classification clear. EEG is especially important for classification of neonatal seizures. What is gained by ignoring the EEG or relegating EEG information to a second-level classifier? It may be of interest to note that our Task Force considered a pure anatomical classification, as limbic, thalamocortical, cortical, brainstem and other seizures, but decided the scientific basis was lacking at this point in time.

Focal vs. Generalized Onset: The division into focal and generalized onset seizures - while not semiologically pure - has great practical value in directing the search for lesions, proper medications and surgical opportunities. The large majority of people with epilepsy will never undergo video-EEG monitoring and will not require categorization of seizure type beyond focal versus generalized. The new unclassified category is a placeholder for our lack of information, rather than a true seizure type, but it emphasizes the need for additional investigations and the need to clarify the seizure type.

Seizure evolution/propagation: The ILAE classification highlights the initial symptom, which may guide imaging and EEG studies as to probable areas involved early in the seizures. Describing the evolution of seizures provides more information on the symptomatic zone, but not necessarily the epileptogenic zone. Lüders and colleagues are correct that our system does not adequately handle classification of seizure evolution. But neither does theirs or any other classification system. We chose the most important propagation patterns and named them, as they note. With thousands of possible propagation patterns for seizures and corresponding sequences of behavior, a new strategy will be needed to succinctly describe them all.

Classification vs. description: Seizures, including their pattern of evolution, require full description, not just a classification. Arguments emerge over where seizure classification ends and free text description begins. We made an attempt to suggest "descriptor" terms for common use. Including all semiological data would result in many hundreds of seizure types. Is it important to consider as different seizure types those with piloerection versus those with flushing?

Applicable age: Lüders et al. comment that ILAE has different commissions for different ages and for status epilepticus. The ILAE seizure classification Task Force, where pediatric representation was considerable, developed a system applicable to children, adolescents, adults and seniors. Although there is ongoing work by an ILAE neonatal seizure commission, even that classification will likely largely be consistent with the ILAE 2017 seizure classification (see draft by Pressler and colleagues [5]).

Aura: Lüders et al. wish to retain the term "aura," which is indeed beloved by the epilepsy community. The problem is that much of the public and even some physicians do not consider an aura to be a seizure, with potentially serious consequences. The first author of this response letter encountered a

patient whose physician stopped seizure medicines because only auras were present, with a resulting lethal car crash. Labeling an "aura" as a "seizure" (which it is) will minimize this misconception.

Redundancy: The authors are correct about avoiding redundancy, but the ILAE Task Force explicitly gave permission in the publication [2] to omit unnecessary words where terms are unambiguous. Perhaps, we should have tabulated a list of such possibilities in order to make this clear. Criticism is made of "cumbersome and imprecise" terminology. In fact, we made an effort to use plain words. The 1981 classification employed obscure terms such as partial, simple partial, complex partial, psychic, which we transmuted to focal, focal aware, focal impaired awareness, cognitive. These terms, unlike, for example, "dialeptic," [4] require little or no explanation. The ILAE 2017 classification can be used by all health professionals - not only epileptologists. To facilitate this, a basic and expanded version are provided, with the latter being an expansion of the former, with more subheadings.

Epilepsy classification: The ILAE classification of the epilepsies includes several dimensions, representing seizure type, epilepsy type (which takes into account multiple seizure types and evolution over time), etiology, comorbidities and syndromes. These are not hierarchical, as is explained in the classification, but add complementary information important for management of the patient's epilepsy. The Lüders suggestion to classify the epilepsies by seizure type, location of the epileptogenic zone, etiology and comorbidities is similar to the proposal of Scheffer et al. [3]. Further detail on location of the epileptogenic zone would be useful in some circumstances, but not necessarily required as a set of individual seizure classifications. We suspect that there would be little consensus about how specific to make location - lobes, gyri, Brodmann areas or networks? Verifying accuracy of seizure classification based on specific location would require successful epilepsy surgery, applicable to only a small fraction of the world's epilepsy population. Lüders and colleagues assert "If the seizure type is known, the epilepsy type becomes a tautology." In fact, the ILAE seizure classification can be used even in patients who have symptomatic or other types of seizures, but not epilepsy [6].

The ILAE 2017 Epilepsy Classification also includes epilepsy syndromes, which are critical for understanding a patient's epilepsy, especially for epilepsies beginning in childhood. Knowledge of both etiology and syndrome are critical for management of people with epilepsy. The patient's clinical picture, prognosis, heritability and therapeutic opportunities depend upon the epilepsy syndrome. We do not consider syndromes "empirical and artificial." Such an assertion ignores the importance of

syndromes, where one genetic etiology often results in a spectrum of epilepsy syndromes that require very different treatment approaches. The clinician needs to consider both genetic findings and syndrome to ensure optimal care for each patient. For example, a child with a *SCN2A* encephalopathy may have a gain-of-function pathogenic variant in the setting of Ohtahara syndrome, while another may have a loss-of-function variant with epilepsy with myoclonic-atonic seizures [7]. Sodium channel blockers are appropriate in the patient with a gain-of-function *SCN2A* encephalopathy but could be dangerous in the patient with a loss-of-function variant.

Requiring "official" terms: The question is reasonably raised about forbidding all terms except those used in the "official" classifications. The authors of the seizure classification paper did not invoke this rule. In fact, we observed that an ideal classification depends upon the user. A surgeon would favor a classification of seizures by location and a pharmacologist by response to various medicines. One size does not fit all. Accurate citation of prior literature may require use of the terminology employed by that publication. The statement by Lüders and colleagues that League journals forbid the use of custom classification terms is incorrect. The League's journals reasonably require that submitted papers use a common language when referring to seizures and epilepsy, so that information in published papers can be directly compared. The journals do not forbid concurrent use of other terms as well, so long as they are mapped (as much as is possible) to the ILAE classification. Without a common language, meta-analyses and other valid scientific reviews cannot reliably be performed.

Value is determined by the user: The 2017 Classification is designed to provide a practical classification to inform epilepsy management in both resource poor (also known as resource normal) and resource rich health care systems; not a classification emphasizing pre-surgical planning, which may be a strong point of the classification proposed by Lüders et al. Ultimately, the value determination of a new classification system is in the hands of the users. One study [8] of 606 Norwegian children with epilepsy found the new classification to allow a higher precision of diagnosis, with a broad syndrome characterization in 93% and a defined syndrome in 37%. An outpatient retrospective review [9] of 200 epilepsy patients found that the 1981 classification resulted in 89 unclassified seizure types, 75% of which subsequently were classified using the 2017 classification. In their view, "The combination of awareness level and motor/non-motor features introduces greater flexibility and allows for detailed seizure description."

Conclusion: Controversy about seizure classifications will continue until science explains why there are different types of seizures. Until then, every classification is a compromise, reflecting consensus and pragmatism. Despite the points raised by Lüders and colleagues, the ILAE Task Force continues to believe that the 2017 classification is a significant step forward for classification of epilepsy in the large majority of patients with epilepsy. Other possible paths, such as those focusing on suitability for epilepsy surgery, will also be valuable as we work towards a final scientific classification.

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.

Disclosures:

Robert Fisher holds stock or options in Zeto, Cerebral Therapeutics, Avails Medical and Smart-Monitor and he consults for Medtronic.

J. French receives NYU salary support from the Epilepsy Foundation and for consulting work and/or attending Scientific Advisory Boards on behalf of the Epilepsy Study Consortium for Acadia, Adamas, Addex, Aeonian, Anavex, Axcella Health, Axovant, Biogen, BioMotiv/Koutif, Blackfynn, Bloom Science, BridgeValley, Cavion, Cerebral Therapeutics,Cerevel, Crossject, CuroNZ, Eisai, Empatica, Engage Therapeutics, Epitel, GW Pharma, Idorsia, Impax, Ionis, J&J Pharmaceuticals, Marinus, Neurelis, Novartis, Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Pfizer, Pfizer-Neusentis, Praxis, Redpin Therapeutics, Sage, Sancillio, Shire, SK Life Sciences, Springworks, Stoke, Sunovion, Supernus, Takeda, UCB Inc., Ultragenyx, Vyera, West Therapeutic Development, Xenon Pharmaceuticals, Xeris, Zogenix, Zynerba. J. French has also received research grants from Biogen, Cavion, Eisai, Engage, GW Pharma, Lundbeck, Neurelis, Ovid, SK Life Sciences, Sunovion, UCB, and Zogenix as well as grants from the Epilepsy Research Foundation, Epilepsy Study Consortium, and NINDS. She is on the editorial board of Lancet Neurology and Neurology Today. She is scientific officer for the Epilepsy Foundation for which NYU receives salary support. She has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Adamas, Axovant, Biogen, Blackfynn, Crossject, CuroNz, Engage, Idorsia, Neurelis, Novartis, Otsuka, Ovid, Pfizer, Redpin, Sage, SK Life Science, Takeda, UCB.

Lieven Lagae received speakers honoraria from and is participating at advisory boards of Zogenix, Livanova, UCB, Eisai, Novartis, NEL and Epihunter.

Solomon L. Moshé is the Charles Frost Chair in Neurosurgery and Neurology and partially funded by grants from NIH U54 NS100064 and NS43209, US Department of Defense (W81XWH-13-1-0180) and the Heffer Family and the Segal Family Foundations and the Abbe Goldstein/Joshua Lurie and Laurie Marsh/ Dan Levitz families. Dr. Moshé is serving as Associate Editor of Neurobiology of Disease and is on the editorial board of Brain and Development, Pediatric Neurology and Physiological Research. He receives from Elsevier an annual compensation for his work as Associate Editor in Neurobiology of Disease and royalties from 2 books he co-edited. He received a consultant fee from Mallinkrodt and UCB. He has no conflicts of interest in regards to this article.

Jukka Peltola has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and Cyberonics; received speaker honoraria from Cyberonics, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel congresses from Cyberonics, Eisai, Medtronic, and UCB; and participated in advisory boards for Cyberonics, Eisai, Medtronic, UCB, and Pfizer.

Emilio Perucca received speaker and/consultancy fees from Biogen, Eisai, GW Pharma, Sanofi, Takeda, and UCB.

Ingrid Scheffer has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia and Xenon Pharmaceuticals; 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, BioMarin, and Eisai; has received funding for travel from Athena Diagnostics, UCB, Biocodex, GlaxoSmithKline, Biomarin 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, and March of Dimes.

E Somerville has no disclosures relevant to this publication but has performed clinical trials for, consulted to, received speaker fees from and/or received travel support from Eisai, UCB Pharma,

Zynerba, SK Life Sciences, Sci-Gen, Marinus, Upsher-Smith, Bial, Novartis, the Epilepsy Study Consortium, the New South Wales Ombudsman and the National Transport Commission of Australia.

Dr. Sperling has consulted for Medtronic, Eisai, and NeurologyLive and has research contracts from SK Life Science, UCB Pharma, Eisai, Neurelis, Medtronic, Takeda, Cavion, and Engage.

S Wiebe has received unrestricted educational grants from UCB Pharma and Eisai.

Elza Márcia Yacubian received speaker fees from Abbott and UCB.

Andreas Schulze-Bonhage, Carol D'Souza, Sheryl Haut, Floor Jansen, Edouard Hirsch, Eliane Roulet-Perez, Sameer Zubieri have nothing to disclose.

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