Epilepsia, 53(Suppl. 2):22–27, 2012
doi: 10.1111/j.1528-1167.2012.03555.x

CLASSIFICATION REVISITED

Neuroimaging in the definition and organization of the epilepsies: We're not there yet

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Summary

Neuroimaging significantly affects the diagnosis and treatment of patients with patients. Despite its importance, magnetic resonance imaging (MRI) has been marginally incorporated into concepts used to define epilepsy etiologies by the International League Against Epilepsy (ILAE) Classification Commission. We propose that Structural etiology be defined as positive neuroimaging abnormalities likely causing the seizures. This would contrast with Genetic and Unknown etiologies, where imaging shows no overt structural abnormality that explains the seizures. It is further recommended that Structural and Metabolic be separated into individual categories, as the outcomes and therapies are different. It is advocated that Structural etiology be subdivided into subgroups based on MRI and surgical syndromes. With this approach, the ILAE should acknowledge that both MRI and electroencephalography (EEG) are necessary diagnostic tools in the classification of epilepsy syndromes and etiologies in the modern era. Promoting the use of neuroimaging into concepts that determine terminology will promote the notion that epilepsy classification should consider structural etiology of the seizures, along with the frequency of the most common epilepsy syndromes, and prognosis for spontaneous and treated remission and cure.

KEY WORDS: MRI, Epilepsy syndromes, Idiopathic, Symptomatic, Cryptogenic, Genetic, Structural, Unknown.

Over the past 35 years, neuroimaging, especially magnetic resonance imaging (MRI), fluorodeoxyglucose–positron emission tomography (FDG-PET), and ictal single photon emission computed tomography (SPECT), has had a profound effect on the diagnosis and management of patients with epilepsy, and epilepsy neurosurgery. Epidemiology studies indicate that lesions likely responsible for the seizures are found in 20–25% of MRI scans from patients with nonidiopathic (nongenetic) epilepsy syndromes (Berg et al., 2009b). Children with positive MRI scans have a younger age at seizure onset, and are more likely to meet the definition of medically refractory epilepsy than those with negative scans (Harvey et al., 2008; Berg et al., 2009b; Kwan et al., 2010). Once a patient has failed adequate trials of two antiepileptic drugs (AEDs), the chance of becoming seizure free with AEDs decreased to <5% for those with positive MRI scans compared with higher rates for patients with negative scans (Berg et al., 2009a; Callaghan et al., 2011). More than 90% of epilepsy surgery patients with medically refractory epilepsy have positive neuroimaging (Harvey et al., 2008). In MRI-negative cases, newer imaging modalities, such as FDG-PET coregistration and subtraction ictal SPECT coregistered to MRI (SISCOM) are identifying occult structural lesions, and complete resection of the lesion is a major predictor of becoming seizure free after surgery (McIntosh et al., 2004; Salamon et al., 2008; Velasco et al., 2011; von Oertzen et al., 2011; Wu et al., 2011).

Despite the documented importance of neuroimaging in the care of patients with epilepsy, MRI and other neuroimaging tools have played a fairly minor role in the conceptual organization and definition of terms used for classifying the epilepsies by etiology. This report reviews the role of neuroimaging in past and current classification schemes proposed by the International League Against Epilepsy (ILAE). Based on that history and the importance of MRI in current practice, we propose changes that better integrate neuroimaging into the organization of the

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epilepsies. It is our position that in the modern era, MRI should be equally available and the findings given equal weight compared with electroencephalography (EEG) and seizure semiology in the organization of epilepsy syndromes and etiology.

Neuroimaging in the ILAE Classification of Epilepsies and Etiology

The ILAE classification of the epilepsies and their subsequent revisions have focused almost exclusively on behavioral semiology and electrophysiologic characteristics, with minimal input from neuroimaging in defining epilepsy syndromes (Commission on Classification and Terminology of the International League Against Epilepsy, 1981, 1985, 1989). This is expected, since the initial concepts that created these schemes were produced before the widespread availability of modern neuroimaging (Gastaut, 1969b,a). Consequently, terms used to define etiology have been impractical for those conducting clinical research at tertiary specialty centers that include neuroimaging and epilepsy neurosurgery. In the 1985 report and 1989 revision, for example, the concept of partial epilepsies (now termed focal) were presumed to be from known or suspected central nervous system (CNS) insults and abnormalities, and were considered symptomatic. The notion was that seizures were secondary in symptomatic epilepsy as compared with primary epilepsy for those with traditional idiopathic etiologies. Despite the availability of computed tomography (CT) and MRI, there was no recommendation by the Commission to confirm the existence of structural lesions in those with symptomatic epilepsy. These limitations to the ILAE classification system were recognized more than a decade ago (Engel, 1998; Everitt & Sander, 1999).

The logic, although reasonable in concept, has correlated poorly with MRI findings in patients with epilepsy. For example, it is estimated that 10–15% of patients with ''symptomatic epilepsy'' have negative MRI scans (Berg et al., 2009b). In addition, using electroclinical criteria, it was determined that some patients with traditional cryptogenic and idiopathic epilepsy often harbored lesions related to their epilepsy (Loddenkemper et al., 2009). This has generated considerable confusion in attempting to identify epilepsy patients with structural lesions as the etiology of their seizures. In the 1989 classification system, patients were considered to have symptomatic etiology if there was a prior history of a presumed CNS insult (e.g., meningitis, trauma) and focal seizures. That patient was still considered to have symptomatic epilepsy even if the MRI and neurologic examination were normal. In addition, it was impossible to separate a patient with the same clinical history but with focal damage to the anterior temporal region rendering that person a possible surgical candidate. Similarly, if patients developed recurrent focal epilepsy without a known prior CNS insult, their epilepsy was generally classified as cryptogenic until the MRI showed a lesion and then they might be reclassified as symptomatic (Shinnar et al., 1999). Furthermore, some patients with generalized epilepsy and seizures starting as infants, such as infantile spasms and Lennox-Gastaut syndrome, were found to have focal cortical lesions by neuroimaging that when surgically removed controlled their seizures (Chugani et al., 1990; Wyllie et al., 1996; Nordli et al., 2001). These findings challenge the central concept of the ILAE classification systems that separates primary from secondary epilepsy.

Proposed Amendments to the 2010 Commission on Classification Report

The 2010 report from the Classification Commission, although better, does not go far enough in incorporating MRI and other neuroimaging techniques into definitions of epilepsy etiology (Berg et al., 2010). In fact, there were essentially minimal changes in the 2010 report to what constitutes the concept of structural compared with symptomatic etiology. As a result, modifications are suggested that better reflect the role and importance of neuroimaging in current clinical practice that has impact for patients. For instance, the 2010 report combined Metabolic with Structural into a single etiology category. This was done to emphasize the difference of genetic from nongenetic etiologies, as the committee focused considerable attention on the future contribution of gene research in identifying epilepsy syndromes. However, that discussion did not consider the current contribution of neuroimaging in determining structural epilepsy etiologies. Grouping metabolic syndromes with structural lesions into a single etiology group does not make sense for practicing epileptologists, as the syndromes and treatments are different. We recommend that Structural and Metabolic etiologies be independent categories in any classification of epilepsy etiology (Table 1).

Another problem with the 2010 report is that a positive MRI was not considered essential and necessary in the definition of epilepsy patients with Structural etiology. In clinical practice, MRI is used just as often if not more frequently than EEG as diagnostic tools in patients with recurrent seizures. In fact, in many parts of the world and in rural America, MRI is more widely available than competent EEG evaluation. Given that one-fifth to one-fourth of patients with epilepsy are MRI positive and if positive such information helps predict response to medical treatment and prognosis, it seems essential that MRI be given equal weight to EEG in the classification of epilepsy

Table 1. Recommended amendments to the 2010 report from classification commission

Amendments to etiology classification
Acknowledge that EEG and MRI are necessary diagnostic tools to classify epilepsy by etiology
Structural and metabolic should be separate etiology categories (not combined)
Structural etiology should be defined as a lesion on MRI (and possibly other neuroimaging modality) likely causing the seizures
Within structural etiology, subgroup most common etiologies by MRI features
Within structural etiology, capture common and rarer epilepsy surgery syndromes under separate subgroup, which incorporates negative MRI but positive histopathology
Unknown etiology should be defined as no known electroclinical syndrome by EEG and no identified etiology by MRI
Genetic etiology should include in the definition that there is no apparent structural lesion responsible for the epilepsy

Table 2. Proposed classification by etiology incorporating MRI

Structural etiology: Positive MRI lesion likely causing epilepsy	Approximate incidence
Genetic primary (fits electroclinical syndrome or genetic mutation; generally negative MRI scan)	
Structural primary	
MRI description	
Atrophic/acquired secondary to injury (e.g., trauma)	40–50%
Malformation of cortical development	20–25%
Discrete lesions (e.g., tumors, cavernomas)	15%
Lesions from genetic mutations (e.g., TSC, NF1)	10%
Others not described above	
Epilepsy surgery syndromes (confirmed by histopathology when possible)	
MTLE from HS	30–40% Adults
Tumors operated	20% Adults and children
Focal cortical dysplasia	30–40% Children
Histopathology negative	
Rarer epilepsy surgery syndromes (examples)	All <5%
Hypothalamic hamartoma	
Rasmussen encephalitis	
Tuberous sclerosis complex	
Hemimegalencephaly	
Sturge-Weber	
Cavernous malformations	
Aicardi syndrome	
Hypomelanosis of Ito	
Ohtahara syndrome	
MRI negative but neuroimaging positive lesions	
Unknown (negative MRI and no identified electroclinical syndrome)	
Focal seizures	
Temporal	To be determined
Frontal	
Parietal	
Occipital	
Generalized nonelectroclinical syndrome	

etiologies. Hence, it is strongly recommended that classification by etiology recognize the importance of obtaining brain MRI, and that by definition all patients classified as Structural have positive scans related to their seizures. This is irrespective of the seizure type as it has become increasingly recognized that patients with discrete brain lesions can have different epilepsy phenotypes often depending on age at seizure onset.

Even with the above proposed changes, it would still be difficult to use the 2010 ILAE report to capture epilepsy surgery syndromes and their histopathologic etiologies. Given the importance of identifying these patients and the lack of appreciation among general physicians and neurologists about treatment options in those with positive MRI scans, this should be changed (Erba et al., 2012). Although one could argue that epilepsy surgery represents a relatively small proportion of patients with epilepsy (roughly 5% of those with new onset seizures), of those with medically refractory epilepsy at a frequency of one seizure per month or greater (about 15–20% of those with epilepsy), from 1:3 to 1:4 will be surgical candidates (Berg et al., 2009b). This is similar in frequency to patients with absence epilepsy and benign epilepsy from centrotemporal spikes (Wirrell et al., 2011). Likewise, identifying and characterizing the incidence and prevalence of potential epilepsy surgical cases has an effect on public health policy and planning health care resources, such as the number and staffing requirements of comprehensive epilepsy centers.

For these reasons, it is urged that the Structural category be organized in a way that captures the most frequent etiologies by MRI characteristics with separate subgroups for the most common epilepsy surgery syndromes and MRI negative but neuroimaging positive (e.g., other modalities such as FDG-PET, SISCOM, magnetoencephalography [MEG]) cases (Table 2). The epilepsy surgery subcategory can incorporate histopathology along with neuroimaging into the classification by etiology, which would help capture subtle substrates into the Structural etiology group. This organization plan anticipates that knowledge gained from newer neuroimaging techniques, such as resting state functional MRI (fMRI), can be more easily incorporated into concepts of etiology (Zhang et al., 2011; Masterton et al., 2012). From existing epidemiology studies, the most common structural etiologies described by MRI are likely acquired associated with atrophic brain lesions (focal or generalized brain atrophy secondary to various insults such as trauma, stroke, birth injury and hemorrhage, porencephalic cysts, infection, and so on), and malformations of cortical development (e.g., lissencephaly, polymicrogyria, and microcephaly) (Barkovich et al., 2005). Less common are structural lesions secondary to genetic mutations (e.g., tubers in tuberous sclerosis

complex, lesions and tumors from neurofibromatosis), and discrete lesions (e.g., low-grade tumors, hypothalamic hamartoma). For epilepsy surgery syndromes, patients with mesial temporal lobe epilepsy from hippocampal sclerosis, seizures from tumors (temporal and extratemporal), and refractory epilepsy from type I and type II focal cortical dysplasia are the most common etiologies (Harvey et al., 2008; Hemb et al., 2010; Blumcke et al., 2011). Rarer syndromes will include a number of etiologies as suggested in Table 2.

Implications of Suggested Changes on Clinical Research and Coding

The inclusion of neuroimaging into the concepts and terminology defining epilepsy etiology has other implications that should be considered by the Commission on Classification and clinical researchers. For example, although it is implied by the way epilepsy syndromes are described that EEG capability is necessary, the 1989 and 2010 Commission on Classification reports do not explicitly state what are the minimal requirements of expertise and diagnostic tools necessary for classifying patients with epilepsy. Clinical criteria alone are usually not enough to fully characterize a person's seizures. Without a witness to the event, the best that probably can be cataloged is whether a person has epilepsy, probable epilepsy, or a paroxysmal disorder of unclear etiology (Thurman et al., 2011). If one accepts that characterizing seizures and epilepsy syndromes requires more than second hand clinical information on semiology, then it is suggested that requirements to use the ILAE classification system be incorporated into the report, and EEG and MRI be included as minimal criteria. An extension of that concept has impact on defining patients placed in the Genetic and Unknown categories. To diagnose someone as having epilepsy of Unknown etiology takes on a more refined definition as a person who has a negative MRI scan and an unidentified electroclinical syndrome (Linehan et al., 2011). Currently, Unknown etiology is not well defined in the 2010 report.

Incorporation of MRI into the definition of etiology has impact on epidemiology studies and the World Health Organization's International Classification of Diseases (WHO-ICD). With few exceptions, nearly all epidemiology studies reported to date and the ICD-9 and ICD-10 codes have not incorporated MRI scans and their results. MRI findings are used in other neurologic classification systems, such as tumors and vascular malformations. Inclusion of MRI in epilepsy diagnosis for population surveys and hospital reporting would provide critical information for clinicians and health care policy makers about the incidence and prevalence of epilepsy patients by specific etiologies.

ILAE Definition of Medically Refractory Epilepsy and Etiology

As previously stated, patients with positive MRI scans are less likely to be controlled on AEDs than those with normal scans. In the future, it might be worth considering inclusion of ILAE's definition of therapy -resistant epilepsy and therapeutic response to medical and surgical treatments as concepts applied in classifying seizures and epilepsy (Kwan et al., 2010). At the end of the day, what patients most want to know is whether there is a treatment for their particular form of epilepsy and what are the chances that therapy will work? If existing treatments, such as currently available AEDs, have the same response regardless of the type of epilepsy or seizure type, the value of that classification system should probably be called into question, and another scheme with greater focus on incidence and prognosis considered (Glauser et al., 2006).

Future Considerations: Etiology versus Causality

The 2010 Commission on Classification report starts the process of organizing epilepsy syndromes as genetic and structural in origin while still recognizing that etiology is unknown in about half of patients with epilepsy (Berg et al., 2010). The report also acknowledges that any classification should be flexible and change as new information becomes available and as problems with the older system are encountered. A long interval passed from 1989 to 2010 between the last two major reports, and it is hoped that further refinements from the ILAE Commission on Classification appear sooner than later. This is especially relevant for neuroimaging, where continued improvements and upgrades can be expected to have clinical impact on patients with epilepsy (Hemb et al., 2010).

As our diagnostic tools improve, we also need to keep in mind that the etiology of a person's epilepsy is not always the same as the ''cause'' of the seizures. This concept may need to be considered as future terms in epilepsy are defined. A patient may have hippocampal sclerosis or cortical dysplasia as the etiology of their epilepsy, but that does not mean we know how the lesion produces seizures. The lesion may alter excitatory and inhibitory synaptic transmission or alter hard wired axonal circuits between the lesion and surrounding cortex. Understanding how genetic and structural abnormalities ''cause'' the brain to have intermittent unprovoked seizures will have greater effect on how we diagnosis and treat patients than just knowing etiology.

Perhaps future classification systems will incorporate a hybrid of existing concepts and methods of diagnosis as

more fundamental ''causes'' of epilepsy are discovered. Such concepts will also have to take into consideration that epilepsy syndromes and networks are probably not static but evolve over the lifetime of a patient. This means understanding how seizures and epilepsy alter brain networks during development, and in matured brains. In other words, the classification of the epilepsies, epilepsy syndromes, and epilepsy etiologies should rely on all available diagnostic methods and concepts, especially if the findings from those studies have bearing on prognosis and treatment of the seizures. Presently, that should include clinical semiology, EEG, and, where appropriate, MRI and other imaging studies.

Acknowledgments

GWM was supported by NIH grant R01 NS38992.

Disclosure

Dr. Mathern serves on the Editorial Board for *Neurology, Epilepsy Research, Epileptic Disorders, and Epilepsy & Seizures,* and on the Data Management Committee for Neuropace, Inc. 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.

References

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. (2005) A developmental and genetic classification for malformations of cortical development. *Neurology* 65:1873–1887.

Berg AT, Levy SR, Testa FM, D'Souza R. (2009a) Remission of epilepsy after two drug failures in children: a prospective study. *Ann Neurol* 65:510–519.

Berg AT, Mathern GW, Bronen RA, Fulbright RK, DiMario F, Testa FM, Levy SR. (2009b) Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. *Brain* 132:2785–2797.

Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshe SL, Nordli D, Plouin P, Scheffer IE. (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 51:676–685.

Blumcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, Jacques TS, Avanzini G, Barkovich AJ, Battaglia G, Becker A, Cepeda C, Cendes F, Colombo N, Crino P, Cross JH, Delalande O, Dubeau F, Duncan J, Guerrini R, Kahane P, Mathern G, Najm I, Ozkara C, Raybaud C, Represa A, Roper SN, Salamon N, Schulze-Bonhage A, Tassi L, Vezzani A, Spreafico R. (2011) The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 52:158–174.

Callaghan B, Schlesinger M, Rodemer W, Pollard J, Hesdorffer D, Allen Hauser W, French J. (2011) Remission and relapse in a drug-resistant epilepsy population followed prospectively. *Epilepsia* 52:619–626.

Chugani HT, Shields WD, Shewmon DA, Olson DM, Phelps ME, Peacock WJ. (1990) Infantile spasms: I. PET identifies focal cortical dysgenesis in cryptogenic cases for surgical treatment. *Ann Neurol* 27:406–413.

Commission on Classification and Terminology of the International League Against Epilepsy. (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 22:489–501.

Commission on Classification and Terminology of the International League Against Epilepsy. (1985) Proposal for classification of epilepsies and epileptic syndromes. *Epilepsia* 26:268–278.

Commission on Classification and Terminology of the International League Against Epilepsy. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 30:389–399.

Engel J Jr. (1998) Classifications of the International League Against Epilepsy: time for reappraisal. *Epilepsia* 39:1014–1017.

Erba G, Moja L, Beghi E, Messina P, Pupillo E. (2012) Barriers toward epilepsy surgery. A survey among practicing neurologists. *Epilepsia* 53:35–43.

Everitt AD, Sander JW. (1999) Classification of the epilepsies: time for a change? A critical review of the International Classification of the Epilepsies and Epileptic Syndromes (ICEES) and its usefulness in clinical practice and epidemiological studies of epilepsy. *Eur Neurol* 42:1–10.

Gastaut H. (1969a) Classification of the epilepsies. Proposal for an international classification. *Epilepsia* 10(Suppl.):14–21.

Gastaut H. (1969b) Clinical and electroencephalographical classification of epileptic seizures. *Epilepsia* 10(Suppl.):2–13.

Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. (2006) ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 47:1094–1120.

Harvey AS, Cross JH, Shinnar S, Mathern GW. (2008) Defining the spectrum of international practice in pediatric epilepsy surgery patients. *Epilepsia* 49:146–155.

Hemb M, Velasco TR, Parnes MS, Wu JY, Lerner JT, Matsumoto JH, Yudovin S, Shields WD, Sankar R, Salamon N, Vinters HV, Mathern GW. (2010) Improved outcomes in pediatric epilepsy surgery: the UCLA experience, 1986–2008. *Neurology* 74:1768–1775.

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J. (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 51:1069–1077.

Linehan C, Tellez-Zenteno JF, Burneo JG, Berg AT. (2011) Future directions for epidemiology in epilepsy. *Epilepsy Behav* 22:112–117.

Loddenkemper T, Cosmo G, Kotagal P, Haut J, Klaas P, Gupta A, Lachhwani DK, Bingaman W, Wyllie E. (2009) Epilepsy surgery in children with electrical status epilepticus in sleep. *Neurosurgery* 64:328–337; discussion 337.

Masterton RA, Carney PW, Jackson GD. (2012) Cortical and thalamic resting-state functional connectivity is altered in childhood absence epilepsy. *Epilepsy Res* 99:327–334.

McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF. (2004) Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain* 127:2018–2030.

Nordli DR Jr, Kuroda MM, Hirsch LJ. (2001) The ontogeny of partial seizures in infants and young children. *Epilepsia* 42:986–990.

Salamon N, Kung J, Shaw SJ, Koo J, Koh S, Wu JY, Lerner JT, Sankar R, Shields WD, Engel J Jr, Fried I, Miyata H, Yong WH, Vinters HV, Mathern GW. (2008) FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. *Neurology* 71:1594–1601.

Shinnar S, O'Dell C, Berg AT. (1999) Distribution of epilepsy syndromes in a cohort of children prospectively monitored from the time of their first unprovoked seizure. *Epilepsia* 40:1378–1383.

Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, Hesdorffer DC, Hauser WA, Kazis L, Kobau R, Kroner B, Labiner D, Liow K, Logroscino G, Medina MT, Newton CR, Parko K, Paschal A, Preux PM, Sander JW, Selassie A, Theodore W, Tomson T, Wiebe S. (2011) Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia* 52(Suppl 7):2–26.

Velasco TR, Wichert-Ana L, Mathern GW, Araujo D, Walz R, Bianchin MM, Dalmagro CL, Leite JP, Santos AC, Assirati JA Jr, Carlotti CG Jr, Sakamoto AC. (2011) Utility of ictal single photon emission computed tomography in mesial temporal lobe epilepsy with hippocampal atrophy: a randomized trial. *Neurosurgery* 68:431–436; discussion 436.

von Oertzen TJ, Mormann F, Urbach H, Reichmann K, Koenig R, Clusmann H, Biersack HJ, Elger CE. (2011) Prospective use of subtraction ictal SPECT coregistered to MRI (SISCOM) in presurgical evaluation of epilepsy. *Epilepsia* 52:2239–2248.

Wirrell EC, Grossardt BR, Wong-Kisiel LC, Nickels KC. (2011) Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study. *Epilepsy Res* 95:110–118.

Wu JY, Salamon N, Kirsch HE, Mantle MM, Nagarajan SS, Kurelowech L, Aung MH, Sankar R, Shields WD, Mathern GW. (2011) Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex. *Neurology* 74:392–398.

Wyllie E, Comair YG, Kotagal P, Raja S, Ruggieri P. (1996) Epilepsy surgery in infants. *Epilepsia* 37:625–637.

Zhang Z, Liao W, Chen H, Mantini D, Ding JR, Xu Q, Wang Z, Yuan C, Chen G, Jiao Q, Lu G. (2011) Altered functional-structural coupling of large-scale brain networks in idiopathic generalized epilepsy. *Brain* 134:2912–2928.