The clinicopathologic spectrum of focal cortical dysplasias:
A consensus classification proposed by an ad hoc Task Force
of the ILAE Diagnostic Methods Commission

The clinicopathologic spectrum of focal cortical dysplasias (FCD) is localized regions of malformed cerebral cortex and are very frequently associated with epilepsy in both children and adults. A broad spectrum of histopathology has been included in the diagnosis of FCD. An ILAE task force proposes an international consensus classification system to better characterize specific clinicopathological FCD entities.

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**Methods:** Thirty-two Task Force members have reevaluated available data on electroclinical presentation, imaging, neuropathological examination of surgical specimens as well as postsurgical outcome.

**Key Findings:** The ILAE Task Force proposes a three-tiered classification system. FCD Type I refers to isolated lesions, which present either as radial (FCD Type Ia) or tangential (FCD Type Ib) dyslamination of the neocortex, microscopically identified in one or multiple lobes. FCD Type II is an isolated lesion characterized by cortical dyslamination and dysmorphic neurons without (Type IIA) or with balloon cells (Type IIB). Hence, the major change since a prior classification represents the introduction of FCD Type III, which occurs in combination with hippocampal sclerosis (FCD Type IIIa), or with epilepsy-associated tumors (FCD Type IIIb). FCD Type IIIc is found adjacent to vascular malformations, whereas FCD Type IIIId can be diagnosed in association with epileptogenic lesions acquired in early life (i.e., traumatic injury, ischemic injury or encephalitis).

**Significance:** This three-tiered classification system will be an important basis to evaluate imaging, electroclinical features, and postsurgical seizure control as well as to explore underlying molecular pathomechanisms in FCD.

**KEY WORDS:** Epilepsy, Seizures, Hippocampal sclerosis, Cortical dysplasia, Neuropathology.

Focal cortical dysplasias (FCDs) were first described in detail by Taylor et al. (1971). They reported on 10 patients with drug-resistant epilepsy who underwent surgical resection (Taylor et al., 1971). Microscopic examination revealed a peculiar histopathology including cortical disorganization, large bizarre neurons, and, in half of the patients, balloon cells. Since then, the term “FCD” has been widely used for a large spectrum of lesions comprising cortical dyslamination, cytoarchitectural lesions, and underlying abnormalities of white matter (Palmini et al., 2004). With ongoing advances in presurgical neuroimaging techniques, more subtle cortical abnormalities can be identified as potential epileptogenic foci. Following surgery, there is often the expectation that the reporting pathologist will identify a corresponding distinct abnormality rather than give a negative report such as “non-specific minor changes or within normal limits.” The pathologist should be able to provide robust and consistent objective criteria for any cortical abnormality with findings that are reproducible and reliable between laboratories. An ad hoc ILAE Task Force (created under the Commissions of Therapeutic Strategies and Pediatrics with follow up in the Commission of Diagnostic Methods) has made an attempt, therefore, to review available literature on clinical presentation, imaging findings, and histopathologic features of distinct clinicopathologic FCD variants and propose a refined clinicopathologic classification system. It is the sincere expectation of our group that this first international consensus classification will be helpful for clinical practice as well as motivating further research strategies to improve our clinical/imaging/histologic and genetic understanding of FCDs.

**Previous Classification Systems of FCDs**

During the last 15 years, different FCD classifications have been introduced. A neuropathologic grading system was proposed (Mischel et al., 1995), which described the spectrum of histopathologic abnormalities in a series of 77 surgical specimens, that is, balloon cells, neuronal cytomegaly, neuronal heterotopia, polymicrogyria, marginal heterotopia, neurons in the molecular layer, heterotopic white matter neurons, and cortical disorganization. In many epilepsy centers, the epileptogenic lesion is diagnosed only by magnetic resonance imaging (MRI) analysis (Barkovich et al., 2005), but yet, there are no highly sensitive imaging parameters available that can reliably differentiate among FCD subtypes. The classification system of a previous working group report is now widely used (Palmini et al., 2004). By this scheme, FCDs can be histopathologically distinguished into Type I and Type II. FCD Type IA referred to architectural disturbances of cortical lamination, and FCD Type IB included also cytoarchitectural abnormalities, that is, hypertrophic (not dysmorphic, see terminology issues below) pyramidal neurons outside layer 5. Dysmorphic neurons are the histopathologic hallmark of FCD Type IIA. Microscopic identification of dysmorphic neurons and eosinophilic balloon cells specifies FCD Type IIB.

**Clinicoradiologic and Pathologic Presentation of FCDs**

FCDs can be located in any part of the cortex. They have variable size and location, and may also affect multiple lobes. FCD Type II is more frequently encountered in extratemporal areas, particularly in the frontal lobe. Unless the area of FCD is large, patients do not have severe neurologic deficits and the main clinical manifestation is epilepsy. Seizures can start at any age (but usually start during early childhood) and are often drug resistant. Seizure semiology depends on the location of the lesion, and patients with both Type I and Type II dysplasias generally present high seizure frequency (Tassi et al., 2002, 2010). They can also exhibit behavioral disturbances, especially those with early onset epilepsy, and whether this occurs more frequently for FCD involving the temporal lobe remains an important issue. The presence of focal, rhythmic epileptiform discharges is the most characteristic feature of the scalp electroencephalography
(EEG) in patients with FCD, frequently showing spatial correlation with the lesion (Gambardella et al., 1996). First, by means of electrocorticography (ECoG) and then with intracerebral recordings, intrinsic epileptogenicity of dysplastic tissue has been demonstrated, particularly in FCD Type II with evidence of a peculiar interictal activity never observed in other forms of MCD (Palmini et al., 1995; Chassoux et al., 2000). In contrast, inconsistencies in the clinical presentation of patients with FCD Type I most likely result from the difficulty to classify them accurately by microscopic inspection (Chamberlain et al., 2009).

The neuroimaging characteristics of FCDs are a very important component of the clinical assessment (Barkovich et al., 2005; Colombo et al., 2009; Lerner et al., 2009). Among reported findings are increased cortical thickness, blurring of the cortical–white matter junction, increased signal on T2-weighted images, a radially oriented linear or conical transmantle stripe of T2 hyperintensity, cortical thinning, and localized brain atrophy. Unfortunately, none of these signs are consistent or completely reliable. For instance, in the immature and unmyelinated brain, increased T2 signal, localized or transmantle, is difficult to identify, as is the cortical–white matter junction blurring: cortical–white matter junction MR blurring is a normal finding during the postnatal stage of brain maturation (Barkovich et al., 1988). Incomplete myelination can also give the appearance of cortical thickening on T2-fluid-attenuated inversion recover (FLAIR) and T1-weighted images, as partially myelinated white matter becomes transiently isointense to cortex. As recently discussed (Colombo et al., 2009), it seems essential to study the brain with true T2-weighted images as well as T1-weighted and T2-FLAIR images. Beyond these limitations of imaging, published data suggest that patients who are diagnosed histopathologically with the same FCD subtype (according to Palmini’s classification system) have different imaging characteristics (Krsek et al., 2008; Lerner et al., 2009). This makes no physical sense, as entities with identical histology should have identical imaging characteristics. In view of the recently described difficulty in reliably diagnosing FCD pathology, especially when mild (Chamberlain et al., 2009), it seems that imaging variability reflects inconsistent histologic diagnoses, likely combined with the fact that different entities have been included together in a single histologic category in the past. We hope that this new classification will allow more consistent histologic–MRI correlations and that better MRI interpretations will guide better management.

The new “FCD classification system” also takes into account insights from experimental neurodevelopmental studies (Battaglia et al., 2009), that is, sustained plasticity and neurogenesis in the postnatal brain, which is compromised by various pathogenic conditions (Coras et al., 2010). Similarly, the “dysmature cerebral developmental hypothesis” suggested that there is partial failure in later phases of cortical development that might explain the distinctive histopathology of CD and that local interactions of dysmature cells with normal postnatal neurons promote seizures (Cepeda et al., 2006). We propose a three-tiered classification system (Table 1) distinguishing isolated FCDs (FCD Types I and II) from variants associated with other (potentially) epileptogenic lesions (FCD Type III). We propose in addition that mild forms of cortical malformations (mMCDs) should be included in the classification, although their clinical impact will need further clarification (see below). Notwithstanding, any classification system using histopathologic examination will rely on sufficient and representative surgical tissue as well as standardized laboratory protocols (see Supporting Information).

### Table 1. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

<table>
<thead>
<tr>
<th>FCD Type I (isolated)</th>
<th>Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)</th>
<th>Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)</th>
<th>Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCD Type II (isolated)</td>
<td>Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa)</td>
<td>Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)</td>
<td></td>
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<tr>
<td>FCD Type III (associated with principal lesion)</td>
<td>Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIia)</td>
<td>Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD Type IIib)</td>
<td>Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD Type IIId)</td>
</tr>
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</table>

FCD Type III (not otherwise specified, NOS): if clinically/radiologically suspected principal lesion is not available for microscopic inspection.

Please note that the rare association between FCD Types IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD Type III variant.
compromising radial migration and maturation of neurons (FCD Type Ia) or the six-layered tangential composition of the neocortex (FCD Type Ib). The combination of both variants will be classified as FCD Type Ic.

Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)

Histopathologic findings
This variant is characterized by abundant microcolumnar organization (most prominent within layer 3). A “microcolumn” is defined by more than eight neurons aligned in a vertical direction (Fig. 1), if (1) the section is cut perpendicular to the pial surface; (2) a 4-μm thin paraffin embedded section is used, (3) NeuN immunohistochemistry is applied, and (4) aligned neurons present with a small diameter and cell size of <250 μm² (Hildebrandt et al., 2005). Microcolumns resemble ontogenetic columns described during normal cortical development (Rakic, 1988). They can be also seen at lower frequency and with fewer neurons in nonepileptic brain samples, as well as in the vicinity of other principal lesions (see below). The border toward white matter is usually less sharply demarcated due to increased numbers of heterotopic neurons. Cellular abnormalities can be encountered in this variant, and include (1) immature small diameter neurons or (2) hypertrophic pyramidal neurons outside layer 5. The diagnosis of FCD Type I variants will need particular attention, however, when studying agranular or dysgranular areas of the temporopolar lobe (Ding et al., 2009).

Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)

Histopathologic findings
Failure to establish a six-layered tangential composition of the isocortex is a hallmark of this variant (and should, therefore, always be used with caution in non–six-layered allo- or proisocortical areas). The entire neocortical architecture may be affected (Fig. 2A) without any recognizable layering (with the exception of layer 1). Other subtypes are restricted to abnormal layering of layer 2, layer 4, or both. Layer 2 can be either missing or is significantly depleted of the characteristic population of small pyramidal neurons. This pattern results in a blurred demarcation between layers 1 and 2, as well as between layers 2 and 3, whose boundaries are very well defined in nonepileptic controls. Layer 4 can also be missing (Fig. 2C) or is obscured and less distinguishable from layers 3 and 5. The border with white matter is usually less sharply demarcated due to increased neuronal cells. Cellular abnormalities can be encountered in this variant, and include (1) immature neurons with a small diameter or (2) hypertrophic pyramidal neurons outside layer 5 or (3) normal neurons with disoriented dendrites. These observations and other cellular alterations requiring sophisticated neuroanatomic techniques are not mandatory, however, to establish the diagnosis of FCD Type I variants.

Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)

This variant refers to those isolated lesions, in which histopathologic inspection reveals both abnormal radial and
tangential cortical lamination. Histopathologic hallmarks are identical to those specified in Histopathologic findings. This FCD variant is diagnosed only as an isolated lesion and not in combination with any other pathology. It has to be clarified in the future, however, whether such lesions occur within patients with more widespread abnormalities linked to mental retardation and/or multiple congenital abnormality syndromes.

**Electroclinical and imaging findings**

A recent series studied 215 consecutive patients with proven histopathologic diagnosis of Type I FCD (according to Palmini’s classification system) and specifically compared electroclinical and imaging findings as well as postsurgical outcome when FCDs occurred isolated or associated with hippocampal sclerosis and tumors (Tassi et al., 2010). Significant differences were found between both FCD cohorts. Isolated FCDs were observed in 31% of this series and characterized by more frequent seizures, negative MRI, multilobar involvement, as well as worse postsurgical seizure control (46% Engel class I). In contrast, associated FCD Type I patients presented with a similar clinical phenotype than those epilepsy patients with HS or with tumors alone (most frequently with temporal lobe involvement).

Further studies using cohorts of isolated FCD Type I variants are required to characterize reliable presurgical MRI signal changes. A recent series examined 18 children (mean age at surgery was 7.6 years) with multilobar FCD Type I and severe drug-resistant seizures (Blumcke et al., 2010). Significantly reduced “hypoplastic” volumes of affected compared to the nonaffected hemispheres were correlated with the occurrence of microcolumns suggesting severe developmental disturbances (and/or retardation) in isolated FCD variants (FCD Type Ia according to the new classification system). The use of diffusion imaging, voxel-based analysis, and measures of blurring of gray–white matter transition may also identify significant abnormalities. A more routine use of high-field MRI scanners and new MRI contrasts as well as [18F]-fluorodeoxyglucose positron–emission tomography (FDG-PET)/MRI coregistration will enhance sensitivity and specificity (Salamon et al., 2008). Techniques such as MR spectroscopy, FDG-PET, or new PET tracers, for example, $^{11}$C-alphamethyl tryptophan, may infer the presence of abnormality, but specificity needs to be established in this particular cohort of patients.

**Perspectives**

Our approach to classify three isolated FCD Type I variants will need reevaluation for its feasibility in clinical practice. As there is still no clue for underlying pathomechanisms, the Task Force is confident that scientific studies addressing more homogeneous groups of FCD variants will improve our understanding of this disease entity.

One limitation of this clinicopathologic classification system has to be also mentioned. If only small, fragmented, or nonrepresentative surgical tissue specimens were submitted for histopathologic diagnosis, the distinction between isolated and associated FCD subgroups and variants will be difficult to obtain. If no specific diagnosis can be achieved,
a descriptive formulation of microscopic features should be given (Fig. S1). We do not recommend the use of “probable or suspect FCD” as diagnostic terms.

**Focal Cortical Dysplasia Type II**

Definition: Focal cortical dysplasia Type II is a malformation presenting with disrupted cortical lamination and specific cytologic abnormalities, which differentiates FCD Type IIA (dysmorphic neurons without balloon cells) from FCD Type IIB (dysmorphic neurons and balloon cells).

**Focal cortical dysplasia with dysmorphic neurons (FCD Type IIA)**

**Histopathologic findings**

The hallmark of this FCD variant is the presence of dysmorphic neurons, which present with a significantly enlarged cell body and nucleus, malorientation, abnormally distributed intracellular Nissl substance, and cytoplasmic accumulation of neurofilament proteins. There are no balloon cells present (to be confirmed by immunohistochemistry). Discrimination of individual cortical layers is almost impossible (with the exception of layer 1). Other cortical layer abnormalities are frequently encountered and should not be separately classified, including abnormal isocortical layer organization adjacent to the main lesion, as well as heterotopic neurons in layer 1 or white matter.

**Dysmorphic neurons** (Fig. 3E,F) were first described by Crome (1957) and Taylor et al. (1971). Dysmorphic neurons are exclusively characterized by the following set of severe cytologic abnormalities: (1) Neuronal cell diameters are significantly enlarged, ranging from 16–43 \( \mu m \) compared to 12–25 \( \mu m \) in normal-appearing pyramidal neurons in layer 3; (2) The cell nucleus diameter is also significantly enlarged, ranging from 15–28 \( \mu m \) compared to 10–18 \( \mu m \) in normal pyramidal cells in layer 3; (3) Nissl substance is aggregated and displaced toward the cell membrane; (4) phosphorylated (antibody 2F11) and nonphosphorylated neurofilament isoforms (SMI-32) accumulate in their...
cytoplasm (Fig. 3E). Cell shape is not a defining hallmark of this peculiar cell type, as these cells can present with pyramidal or interneuronal phenotypes. Dysmorphic neurons can be distributed throughout the entire cortical thickness or locate within the white matter. The demarcation from FCD Type IIa toward adjacent normal-appearing neocortex is variably ranging from a “sharp” to “smooth” transition. In the latter examples, isolated dysmorphic neurons can be identified distant from the core of the main lesion. In addition, multiple FCD Type II lesions have been recognized individually contributing to seizure generation (Fauser et al., 2009).

Cortical dyslamination (Fig. 3D) is always present. It differs from that described for FCD Type I, in which individual cortical layers are obscured or cortical thickness may be decreased. In FCD Type II, there is no identifiable cortical layering except layer 1. Whether cortical thickness is normal or increased remains to be clarified but it is likely not changed significantly (Andres et al., 2005; Chandra et al., 2007). One obvious difficulty is, however, to delineate the precise border between cortex and white matter. In addition, thickness measurements need always to be performed at the “center of lesion” rather than being randomly selected.

Junction at gray/white matter is usually blurred with increased heterotopic neurons in white matter. These neurons may also be dysmorphic. The precise border between cortex and white matter is usually difficult to delineate.

### Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)

**Histopathologic findings**

The hallmark of this FCD variant is the presence of dysmorphic neurons (significantly enlarged with accumulation of neurofilament proteins) and balloon cells (Sisodiya et al., 2009). Cortical lamination is frequently disrupted with the exception of layer 1 (Fig. 4E). The myelin content may also be altered in underlying subcortical white matter. Other cortical layer abnormalities are frequently encountered and should not be separately classified, including abnormal isocortical layer organization adjacent to the main lesion, as well as heterotopic neurons in layer 1 or white matter. Histopathologically similar lesions are observed in cortical tubers and other gross MCDs, that is, hemimegalencephaly or schizencephaly.

**Balloon cells** present with a large cell body and opalescent glassy eosinophilic cytoplasm [using hematoxylin and eosin (H&E) stain], which lacks Nissl substance (Fig. 4H). Multiple nuclei are often present, and small nuclei may be joined by nuclear “bridges.” Balloon cells can occur at any cortical location (including layer 1) and are often found in the underlying white matter. Balloon cells may gather in small aggregates but can also be found displaced within adjacent “normal” brain tissue. Balloon cells commonly accumulate intermediate filaments vimentin and nestin (Garbelli et al., 1999; Urbach et al., 2002). They have variable glial fibrillary acidic protein (GFAP) and neurofilament staining patterns. In rare examples, coexpression of both markers was reported suggesting glial and neuronal lineage determination, that is, intermediate cells (Talos et al., 2008). Balloon cells may also express the GFAP-delta variant (Martinian et al., 2009), or other stem cell markers, that is, SOX2, CD133, beta-1 integrins, or the onco-fetal antigen CD34 (Fauser et al., 2004; Yasin et al., 2010). Balloon cells and giant cells have gross histomorphologic similarities [according to NIH Consensus Meeting in 2000: (Hyman & Whitemore, 2000)], and which can be observed in cortical tubers from patients with tuberous sclerosis complex (TSC). Despite the similarities between both cell types, which may not be distinguishable by routine histomorphologic workup, we will refer to the term “balloon cell” in our classification to specify this cell population in FCD Type IIb.

**Dysmorphic neurons.** There is no obvious cytologic difference between dysmorphic neurons observed in FCD Type IIa or Type IIb (Figs 3F vs. 4F).

**Intermediate cells.** In vitro electrophysiologic recordings as well as immunohistochemical analysis showed a broad spectrum of abnormal membrane properties and phenotypic specifications in cells obtained from surgical FCD Type IIb lesions. Whereas balloon cells mostly presented with glial-like features, dysmorphic neurons (pyramidal-like or interneuronal-like variants) revealed atypical hyperexcitable intrinsic membrane properties (Cepeda et al., 2006; Andre et al., 2007). Hence, there is a rare cell type, which shares glial and neuronal features and which may be defined as “intermediate-like” cells, as already shown in TSC (Talos et al., 2008).

**Cortical dyslamination.** Like in Type IIa, cortical dyslamination is a hallmark of FCD Type IIb, and the border toward layer 1 often remains visible (Fig. 4E).

**Borders between gray and white matter.** The boundary between gray and white matter is always blurred in FCD Type IIb.

**Altered myelin content in white matter.** There is usually a reduction of myelin staining in the underlying white matter, which can be histochemically verified using Luxol-Fast-Blue or similar appropriate staining protocols during routine neuropathologic workup of surgical specimens (Fig. 4D). However, to date there are no published data available clarifying the origin of reduced myelin content or suggesting significant differences between FCD subgroups.

**Imaging**

FCD Type IIb is often characterized by hypo-, de-, or dysmyelination in the subcortical white matter. On T1-weighted images, such changes cause blurring of the gray–white matter junction and mimic increased cortical thickness (Colombo et al., 2009). Increased subcortical white matter signal is visible on T2-weighted images and T2-FLAIR images (Fig. 4A). However, the cortex can be seen to have...
normal thickness on T2-weighted images. The white matter signal alterations frequently taper from the crown of a gyrus or bottom of a sulcus toward the ventricle, reflecting the involvement of radial glial–neuronal units. This “transmantle sign,” first described by Barkovich in 1997, is almost exclusively found in FCD Type IIb, but its detection depends largely on an optimized angle and thin MRI sectioning (Barkovich et al., 1997). Blurring between cortex and white matter on T1-weighted and T2-FLAIR images is often more pronounced than in FCD Type I. Frequently, the border appears sharp on T2-weighted images. Abnormal cortical gyration and sulcation, better evaluated on three-dimensional (3D) surface rendering, are frequent findings in FCD Type IIb, and sometimes focal enlargement of the subarachnoid spaces seems to point to the dysplastic lesion, assisting in the diagnosis. In contrast, FCD Type IIa is not always detected on in vivo MRI and is harder to identify than FCD Type IIb.

Clinical and electrophysiologic findings

Data suggest that individuals with FCD Type II coming to surgery have a younger age of seizure onset, shorter
epilepsy duration, and increased seizure frequency compared to FCD Type I (Palmini et al., 2004; Fauser et al., 2006, Lerner et al., 2009), although not consistently (Kresk et al. 2009); these factors will also be influenced by the extent of the lesion. Seizure presentation itself will be age and location related. There is a characteristic interictal intralaminon electrical activity detectable in FCD Type IIb. Intracerebral recordings (stereo-EEG) are usually characterized by total absence of background activity and a distinctive pattern of repetitive, high amplitude, fast spikes, followed by high amplitude slow waves, interspersed with relatively flat periods. Repetitive bursts of low-amplitude high frequency oscillations interspersed with flat periods can also be seen. Similar patterns can be obtained from subdural and epidural (sometimes also by surface) EEG recordings. During drowsiness and slow sleep, fast spikes become more prominent, increase in frequency, and tend to spread into contiguous nonlesional areas (Nobili et al., 2009). During rapid eye movement (REM) sleep, there is a marked decrease in electrical abnormalities.

**Perspectives**

A yet-unresolved issue addresses the clinical differentiation between FCD Type IIa and Type IIb, with respect to history, seizure presentation, electrophysiologic findings, MRI features, or surgical procedures and postsurgical seizure control after complete lesionectomy. If no such differences can be identified in the future, the distinction between both variants will need careful reconsideration. Yet the histopathologic distinction between FCD Type IIa and Type IIb may be problematic, if nonrepresentative or small surgical specimens were submitted for microscopic inspection. New biomarkers including imaging, immunohistochemical stainings, or genetic profiling may be helpful for resolving this obstacle.

Abnormal cortical lamination will be detectable in the vicinity of both FCD Type II variants. We are presently considering this association as a part of FCD Type II and not as a separate FCD Type III subtype, although we cannot exclude a specific role in epileptogenesis. In rare cases, FCD Type IIa or IIb will occur with other principal lesions, that is, hippocampal sclerosis, cavernomas, or tumors. We want to state explicitly that this association is classified as “Dual” or “Double” pathology (see Supporting Information on terminology issues) but not as FCD Type III variant.

**Focal Cortical Dysplasia Type III**

Definition: Focal cortical dysplasia Type III refers to cortical lamination abnormalities associated with a principal lesion, usually adjacent to or affecting the same cortical area/lobe. Four variants should be distinguished: FCD Type IIIa associated with hippocampal sclerosis; FCD Type IIIb associated with tumors; FCD Type IIIc associated with vascular malformations; and FCD Type IIId associated with any other principal lesion acquired during early life.

**Focal cortical dysplasia associated with hippocampal sclerosis (FCD Type IIIa)**

**Histopathologic findings**

In this variant the temporal cortex shows alterations in architectural organisation (cortical dyslamination) or cytoarchitectural composition (hypertrophic neurons outside layer 5) in patients with hippocampal sclerosis (HS, syn. Ammon’s horn sclerosis). The etiology and pathogenesis of FCD Type IIIa remains to be determined but is likely related to the pathogenesis or effect of HS. Note that we do not consider HS with FCD Type IIIa as “Dual Pathology” (see Supporting Information).

The following patterns should be recognized as FCD Type IIIa variants:

1. HS with architectural abnormalities in the temporal lobe, that is, loss of layers 2 or 4. This category also includes the occurrence of hypertrophic neurons outside layer 5, which still share a pyramidal morphology and accumulate phosphorylated neurofilaments. This histopathologic variant may not be very different from isolated FCD Type I.
2. HS with temporal lobe sclerosis (TLS) (Thom et al., 2009).
3. HS with TLS and heterotopic neurons in subcortical white matter.
4. HS with TLS and small “lentiform” heterotopias in subcortical white matter.
5. HS with small “lentiform” heterotopias in subcortical white matter.

The following patterns should not be included as FCD Type IIIa variants:

1. Neuronal cell loss confined to hippocampus, amygdala, or entorhinal cortex, that is, mesial temporal sclerosis (MTS)
2. HS with heterotopic neurons in the deep white matter of temporal lobe, but no other architectural alteration. Neuronal heterotopia includes also blurring of gray/white matter junction. The pathogenic and epileptogenic significance of this frequent finding has yet to be clarified.
3. HS and any other principal lesion in the temporal lobe, that is, tumors, FCD Type IIa/IIb, vascular malformations, glial scars, or MCDs (other than FCD Type IIIa) should be classified as “Dual Pathology.”

**Temporal lobe sclerosis**

In HS patients, an abnormal band of small and clustered “granular” neurons can be observed in the outer part of layer 2 in approx. 10% of temporal lobe surgical specimens, designated as TLS (Garbelli et al., 2006; Thom et al., 2009). TLS is likely to present severe neuronal cell loss in layers 2 and 3 with associated laminar gliosis.
(GFAP-positive astrogliosis; Fig. 5C) and cortical reorganization. Horizontal bundles of myelinated axons can be observed to a variable degree in these cases using H&E Luxol-Fast-Blue stainings. In 40% of HS/TLS cases more severe involvement of the temporal pole is seen, whereas extensive involvement throughout the temporal lobe occurs in 20%. There is no correlation between this FCD variant and MRI findings in these patients.

Small ‘lentiform’ heterotopias or heterotopic neurons in white matter

In HS patients, small ‘lentiform’ nodular heterotopias can be identified within the temporal lobe (Fig. 6E,F). They usually remain undetected by MRI (Meroni et al., 2009). Radial orientation along the gray/white matter junction is characteristic and cellular composition is usually formed by projecting neurons. These small ‘lentiform’ heterotopias are distinct from the larger nodular heterotopias, which are readily identified by MRI, may be present in any location of the white matter, and are histologically characterized by projecting and local circuit neurons (Meroni et al., 2009). A diagnostic pitfall results from a similar normal anatomic structure located within the depth of the temporal lobe close to the claustrum. Another frequent alteration presents with isolated heterotopic neurons either at (1) the gray/white matter junction (Fig. 6C) or (2) in deep subcortical white matter location (Fig. 6D). Both findings are often encountered in surgical specimens obtained from epilepsy patients, although its pathogenic or epileptogenic significance remains undetermined.

Hypertrophic neurons

In temporal lobe specimens obtained from patients with HS, hypertrophic neurons accumulating phosphorylated or nonphosphorylated neurofilament proteins can be observed in layers 2, 3, or 4 (see Appendix and Fig. 10). In normal ‘control’ human cortex, these pyramidal neurons are usually allocated to layer 5. [Please note that staining intensities with nonphosphorylated neurofilament protein (NFP) antibodies (i.e., SMI 32) increase with age and that neuronal hypertrophy can be observed also in non–epilepsy-related pathologies.

Focal cortical dysplasia associated with tumors (FCD Type IIIb)

Histopathologic findings

The histopathologic hallmark of this new FCD variant is an altered architectural (cortical dyslamination, hypoplasia without six-layered structure), and/or cytoarchitectural composition (hypertrophic neurons) of the neocortex, which occur adjacent to tumors (ganglioglioma, dysembryoplastic neuroepithelial tumor (DNT, syn. DNET), or other epilepsy-associated neoplasms [for review see (Blumcke, 2009)]. It is important to exclude tumor infiltration in areas of cortical abnormalities before establishing the diagnosis of FCD. The etiology and pathogenesis of FCD Type IIIb remains to be determined, but it is likely an acquired process. It should not be considered, therefore, as “Double Pathology” (see Supporting Information).

From a histopathologic standpoint cortical architecture may be severely disturbed (infiltration by tumor cells need to
be excluded) with a small cortical ribbon (hypoplasia) and effacement of six-layered organization (Fig. 7B). We cannot exclude, that the compromised cortical architecture results from an acquired dysplasia secondary to the development of the principal lesion. Notwithstanding, seizure activity may arise from altered networks in this affected cortical area.

Focal cortical dysplasia associated with vascular malformations (FCD Type IIIc)

**Histopathologic findings**

Alterations in architectural (cortical dyslamination, hypoplasia) or cytoarchitectural composition (hypertrophic neurons) occurs adjacent to vascular malformations (cavernomas, arteriovenous malformations, leptomeningeal vascular malformations, telangiectasias, meningioangiomatosis). The etiology and pathogenesis of FCD Type IIIc remains to be determined, but is likely an acquired process. It should not be considered, therefore, as “Double Pathology.”

The histopathologic pattern is similar to that described for other FCD Type III variants, and can be identified adjacent to the principal lesion. Cortical architecture may be severely disturbed (Fig. 8B). However, we cannot exclude the possibility that the compromised cortical architecture is acquired secondary to the development of the principal lesion, but seizure activity may arise from altered networks in this affected cortical area (Ferrier et al., 2007).

FCDs may be associated with abnormal sulcation and are drained by a single, large vein. This might be interpreted as a venous angioma on MRI scans. If the suspected angioma cannot be verified by histopathologic examination, the FCD likely occurs as “isolated” lesion and should be classified as FCD Type I or Type II variant, respectively.

Focal cortical dysplasia associated with other lesions acquired during early life (FCD Type IIIId)

**Histopathologic findings**

The histopathologic hallmark of this new FCD variant is an altered architectural (cortical dyslamination, hypoplasia without six-layered structure) or cytoarchitectural composition (hypertrophic neurons) of the neocortex, which occurs adjacent to other lesions acquired during early life (not included into FCD Type IIIa–c). These lesions comprise a large spectrum including traumatic brain injury (Lombroso, 2000; Marin-Padilla et al., 2002), glial scarring after prenatal or perinatal ischemic injury or bleeding (Fig. 9), and inflammatory or infectious diseases, that is, Rasmussen encephalitis, limbic encephalitis, or bacterial or viral infections.

Focal cortical dysplasia associated with clinically suspected principal lesion, but lesion not available for histopathologic examination (FCD Type III, not otherwise specified, NOS)

If FCD Type I patterns are histopathologically detected in a patient with a clinically suspected principal lesion, but (1) the principal lesion is not available for microscopic

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**Figure 6.**

Histopathologic findings in FCD Type IIIa (small “lentiform” heterotopia and heterotopic neurons with blurring of white matter boundary). (A) The boundary between gray and white matter is very sharp in normal-appearing neocortex. (B) Heterotopic neurons are a rare finding in normal deep white matter (Rojiani et al., 1996). (C) Blurring of the gray–white matter boundary in a surgical temporal lobe specimen obtained from a 39-year-old female patient with drug-resistant MTLE and hippocampal sclerosis. MRI signaling within the temporal lobe was reported normal. (D) Increased numbers of heterotopic neurons can be often observed in deep subcortical white matter (Emery et al., 1997). Same patient shown in C. (E) A rare finding is the observation of small “lentiform” heterotopias in the white matter of the temporal lobe obtained from a patient with HS. This abnormality was not reported by MRI prior to operation. (F) Synaptophysin staining of “lentiform” heterotopias shown in E. Scale bar in B = 200 μm, applies also to A, C, and D. Scale bar in F = 500 μm, applies also to E. MAP2-immunoreactivity in A–D. Four micrometers of paraffin-embedded sections counterstained with hematoxylin.

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inspection (entire sample should be embedded and sectioned for microscopic inspection), or (2) tissue may not be available for microscopic analysis after the surgical procedure, the neuropathologic diagnosis of FCD Type III (NOS) should be considered (Fig. S1).

Clinical and electrophysiologic presentation in FCD Type III

The cohort of HS patients with FCD Type IIIa has not yet been characterized with respect to clinical presentations and electroclinical findings. Previous studies have described some of these patients, with respect to the generation of ictal and interictal activity (Maillard et al., 2004; Chabardes et al., 2005). Another study (Fauser & Schulze-Bonhage, 2006) specifically correlated ictal onset patterns in temporal lobe epilepsy patients with respective histopathology, that is, HS and FCD Type I (according to Palmini’s classification system). Approximately 40% of seizures arise from the amygdala/hippocampus complex, 35% from the temporal neocortex (including the cortical dysplasia), 22% were simultaneously recorded from both sites, and 2% from other regions. The ictal patterns obtained from FCDs in the temporal regions were similar to those seen over extratemporal areas. This study showed that dysplastic tissue in the temporal neocortex is often epileptogenic (Fauser & Schulze-Bonhage, 2006).

Perspectives

Meta-analysis of studies addressing the clinical presentation and histopathologic alterations in patients with FCD Type I (according to previous Palmini classification) demonstrate a very large variability (Blumcke et al., 2009). Postsurgical outcome was also less comparable between studies, with a broad range of Engel 1 seizure control in 21–67% of operated patients. One obstacle is that different cohorts were included, that is, children versus adults and isolated versus HS-associated
FCD variants. The data suggest, therefore, that different clinicopathologic entities were encountered within the Palmini classification of FCD Type I. The major objective of the proposed new FCD classification system is to separate these different entities (FCD Type I vs. Type III). The most reliable strategy to classify these subtypes is a histopathologic distinction between isolated and associated FCD subtypes (Spreafico & Blumcke, 2010). Yet, the histopathologic distinction between isolated and associated FCD variants remains problematic if nonrepresentative or small surgical specimens were submitted for microscopic inspection. The development
of new and reliable biomarkers will be helpful in resolving this obstacle.

We also need to address the issue of whether FCD Type IIIa is an acquired pathology with accompanying reorganization dysplasia resulting from hippocampal sclerosis, rather than being a distinct pathologic entity. The latter would favor the hypothesis that HS is the consequence of chronic epileptogenicity of the temporal lobe due to the dysplasia. Several aspects argue for a common etiology between HS and FCD Type IIIa. Patients from both groups have a similar age at onset and a similar history of febrile seizures as an initial precipitating injury (Marusic et al., 2007); no other clinical differences have yet been identified between isolated HS and HS/FCD Type IIIa cases (Thom et al., 2009). Accordingly, postsurgical outcome is similar in patients with HS only and with FCD Type IIIa (Tassi et al., 2010). Notwithstanding, a standardized histopathologic evaluation of HS patterns also needs to be established by an international consensus. Atypical HS variants should be histopathologically identified, that is, predominant pyramidal cell loss in only CA4 or CA1 regions, as they may associate with a less favorable postsurgical outcome (Blumcke et al., 2007) or may account for the different types of temporal lobe seizures in TLE patients (Kahane & Bartolomei, 2010).

Reorganization of the cortical cytoarchitecture can be observed adjacent to a destructive cortical pathology including an infarct, chronic encephalitis, traumatic brain injury, or vascular malformation (Hart et al., 1998; Kremer et al., 2002; Marin-Padilla et al., 2002). It is likely to be a reflection of the ongoing plasticity and response to injury of the maturing as well as adult cortex. If acquired in the early years there are likely to be additional abnormalities of the

Figure 10.
Abnormal cell types in FCD. Representative examples of abnormal cell types in FCD variants. All images were taken at same magnification (scale bar in B = 50 μm) using recommended immunohistochemical markers (see Table S2). Four micrometers of paraffin-embedded and formalin fixed specimens. (A, B) Biopsy control samples from layer 3 (in A) and layer 2 (in B). (C) A dysmorphic neuron accumulating nonphosphorylated neurofilaments (antibody SMI 32) in a FCD Type IIb specimen. Also note significantly enlarged nucleus with prominent nucleolus. (D) This hypertrophic pyramidal neuron was observed at the border between layers 2 and 3 in an FCD Type IIIa specimen. (E) Microcolumn with alignment of immature, small diameter neurons. FCD Type Ia specimen. (F) In gangliogliomas, dysplastic neurons show bizarre morphology and multiple nucleoli.

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myeloarchitecture. Such acquired dysplasias should be distinguished from primary dysplasias. We believe that the term “progressive cortical dysplasia” (Marin-Padilla et al., 2002) may be misleading and should be replaced by FCD Type IIId.

Architectural or cytoarchitectural disorganization can always be identified in the vicinity of gross malformations of cortical development, that is, with polymicrogyria, hemimegalencephaly, schizencephaly, nodular heterotopia, or cortical tubers. We, therefore, suggest not including these abundant architectural and/or cytoarchitectural disorganization patterns as specific FCD Type III variants until studies show that the presence of such dysplasias relate to divergent clinical outcome.

In rare cases, FCD Type IIA or Type IIB will occur with other principal lesions, that is, cavernomas or tumors. We want to state explicitly, that this association is classified as “Double” pathology (see Supporting Information on terminology issues) but not FCD Type III variant, as both lesions have most likely an independent pathogenesis. The same applies for the rare association between FCD Type IIA/IIB with hippocampal sclerosis, which should be classified as “Dual Pathology,” although this important issue will need further scientific elaboration.

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Disclosure

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. The remaining authors have no conflicts of interest to disclose.

References


large. They are disoriented in the cortex with abnormal aggregates of Nissl substance and phosphorylated or non-phosphorylated neurofilament accumulation in cytoplasm. They mostly represent altered pyramidal neurons but can also show features consistent with those of interneurons.

_Hypertrophic neurons_ resemble large pyramidal cells of layer 5 abnormally located in layers 1, 2, 3, or 4. Dendrites’ orientation and arborization may be altered, but there is no obvious intracellular pathology affecting the nucleus or Nissl substance.

_Immature neurons_ develop from neuroblasts and have a small diameter and cell size (<250 μm²). They do not accumulate nonphosphorylated neurofilaments. They are observed in large numbers in vertically oriented microcolumns (FCD Type Ia).

_Dysplastic neurons_ are the neuronal components of glioneuronal tumors, that is, gangliogliomas and dysembryoplastic neuroepithelial tumor.

_Balloon cells_ have a large cell body with opaque eosinophilic cytoplasm that lacks Nissl substance on Hematoxylin and Eosin stains. They rarely express cytoplasmic/immunohistochemical differentiation with glial (GFAP) or neuronal markers (NFP). Multiple nuclei can be seen.

_Footnote:_ There is considerable debate regarding the terminology used for abnormal cell types, which has been inconsistently used in previous classification systems. The following definitions were based on microscopic inspection of 4–7 μm thin sectioned, formalin-fixed and paraffin-embedded surgical specimens. Representative examples were given in Fig. 10.

**Glossary of terminology**

To avoid the confusion that has been created by various uses of descriptive and diagnostic terms pertaining to malformations of cortical development, we utilize in this revised classification system the following definitions:

_Dysplasia (synonymous with dysgenesis and malformation):_ This is a general term referring to any tissue that is imperfectly developed in embryonic or fetal life. However, dysplasia is a diagnostic term used here to identify specific malformations of the cortex, the so-called focal cortical dysplasias (FCDs), irrespective of their diverse histologic appearances that are addressed by this classification system.

_Heterotopia:_ misplaced tissue or cells within their normal organ of origin.

_Hamartoma_ is a tumor-like non-neoplastic mass (>1 mm) of malformed tissue (Wolf & Wiestler, 1993), composed of normal cells in their normal site that exhibit disorganized architecture. A hamartia is a small glioneuronal lesion that is not grossly visible (<1 mm).

_Ectopia_ is a normally formed organ or tissue in an abnormal site within the body. We do not refer to this definition in our classification system.

_Dyslamination_ is a compromised tangential or radial organization of cortical architecture. It may be observed in any of the proposed FCD subtypes.

_Dual Pathology_ is not yet comprehensively defined (Cendes et al., 1995), and is still ambiguously used in clinical and histopathologic practice. We propose the following definition: Dual Pathology refers only to patients with hippocampal sclerosis, who have a second principal lesion affecting the brain (which may be located also outside the ipsilateral temporal lobe), that is, tumor, vascular malformation, glial scar, limbic/Rasmussen encephalitis, or MCD (including FCD Type IIa/IIb). Ipsilateral temporopolar atrophy with increased T₂ signal changes on MRI is not included as its histopathologic correlate has yet to be specified. Of note, histopathologically confirmed architectural abnormalities in the temporal lobe associated with HS should not be diagnosed as FCD Type I or “Dual Pathology” but FCD Type IIIa.

_Double Pathology_ refers to two independent lesions affecting one or multiple lobes, but not including hippocampal sclerosis. This definition assumes that both lesions evolve from an independent pathogenesis, i.e. a cavernoma in one cerebral hemisphere and a ganglioglioma in the other. Electrophysiology will be necessary to characterize the “most likely” epileptogenic lesion.

_Principal lesions_ comprise any anatomical lesion with etiologically defined pathogenesis of either neoplastic, genetic, infectious, traumatic or metabolic origin. This includes the spectrum of epilepsy-associated tumors, vascular malformations, MCDs, encephalitis, traumatic scars, bleeding, vascular infarction, mitochondrial/metabolic dysfunction and genetic syndromes.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Mild malformations of cortical development (mMCDs).

**Figure S1.** Flow chart for histopathologic examination.

**Table S1.** Definitions of mild MCDs.

**Table S2.** Histochemical and immunohistochemical stains recommended for the histopathologic work-up of surgical FCD specimens.

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