Good interobserver and intraobserver agreement in the evaluation of the new ILAE classification of focal cortical dysplasias


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SUMMARY

**Purpose:** An International League Against Epilepsy (ILAE) consensus classification system for focal cortical dysplasias (FCDs) has been published in 2011 specifying clinicopathologic FCD variants. The aim of the present work was to microscopically assess interobserver agreement and intraobserver reproducibility for FCD categories among an international group of neuropathologists with different levels of experience and access to epilepsy surgery tissue.

**Methods:** Surgical FCD specimens covering a broad histopathology spectrum were retrieved from 22 patients with epilepsy. Three surgical nonepilepsy specimens served as controls. A total of 188 slides with routine or immunohistochemical stainings were digitalized with a slide scanner to allow Internet-based microscopy review. Nine experienced neuropathologists were invited to review these cases twice at a time gap of 3 months and different orders of case presentation. The 2011 ILAE FCD consensus classification served as instruction. Kappa analysis was calculated to estimate interobserver and intraobserver agreement levels. In a third evaluation round, 21 additional neuropathologists with different experience and access to epilepsy surgery reviewed the same case series.

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Interobserver agreement was good ($\kappa = 0.6360$), with 84% consensus of diagnoses during the first evaluation (21 of 25 cases). Kappa values increased to 0.6532 after reevaluation, and consensus was obtained in 24 (96%) of 25 cases. Overall intraobserver reproducibility was also good ($\kappa = 0.7824$, ranging from 0.4991 to 1.000). Fewest changes in the classification were made in the FCD type II group (2.2% of 225 original diagnoses), whereas the majority of changes occurred in FCD type III (13.7% of 225 original diagnoses). In the third evaluation round, interobserver agreement was reflected by the level of experience of each neuropathologist, with $\kappa$ values ranging from moderate (0.5056; high level of experience >40 cases/year) to low (0.3265; low level of experience <10 cases/year).

Significance: Our study achieved a good and reliable interobserver agreement among the group of expert neuropathologists originally involved in the ILAE FCD consensus classification system. Intraobserver reproducibility in this group was even more robust. These results showed considerable improvement compared to a previous study evaluating the 2004 Palmini FCD classification.

Agreement levels were lower in our second group of neuropathologists and were related to their level of access and experience with epilepsy surgery specimens. These results suggested that the more precise ILAE definition of FCD histopathology patterns improves operational procedures in the diagnosis of FCDs. On the other hand, microscopic assessment of FCD is a challenge and requires sustained experience and teaching. The virtual slide review system allowed testing of this hypothesis and reached a widespread group of participating colleagues from different centers all over the world. We propose to further use this tool as a teaching device and also to address other epilepsy-associated entities still difficult to classify such as hippocampal sclerosis, long-term epilepsy-associated tumors, or mild malformations of cortical development (mMCDs), which were not yet covered by current ILAE classification systems.

**Key Words:** Brain, Epilepsy, Neuropathology, Classification, Agreement, Reproducibility.

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Focal cortical dysplasias (FCDs) are localized malformations of cortical development (MCDs) frequently associated with drug-resistant epilepsies. Since the first description of an FCD by Taylor et al. (1971), a variety of clinical, imaging, and histopathologic classification systems have been proposed (Mischel et al., 1995; Palmini et al., 2004; Barkovich et al., 2005). Different terminology use and discrepant clinicopathologic outcome prediction requires, however, international consensus agreement (Blumcke et al., 2009). The ad hoc International League Against Epilepsy (ILAE) Task Force of the Diagnostic Methods Commission reviewed available data on clinical presentation, imaging, and histopathology patterns to describe distinct FCD variants and proposed a refined clinicopathologic classification system (Blumcke et al., 2011). This 2011 ILAE classification includes three FCD categories: FCD type I refers to abnormalities in cortical architecture as defined by radial microcolumns (FCD type Ia), tangential layer alterations (FCD type Ib), or by a combination of both (FCD type Ic). FCD type II is identical to that described by Taylor et al. (1971), histopathologically specified by large and dysmorphic neurons and further subdivided by the absence or presence of balloon cells into FCD type IIa or FCD type IIb, respectively. FCD types I and II generally occur as “isolated” cortical malformations not associated with any other brain lesion. A major challenge in the ILAE classification system was, however, the introduction of FCD type III associated with other principal lesions, that is, hippocampal sclerosis (FCD type IIla), epilepsy-associated tumors (FCD type IIlb), vascular malformations (FCD type IIlc), or any other lesion acquired during early prenatal or postnatal period, for example, trauma, ischemic injury, and encephalitis (FCD type IIIId). Previous studies suggested this feature as an important clinical predictor for long-term postsurgical seizure control (Tassi et al., 2010). As an example, excellent seizure control was reported in 70–100% of patients with FCD type IIb (Urbach et al., 2002; Krsek et al., 2009). On the other hand, postsurgical outcome is less beneficial (21–67%) in Palmini’s previous FCD type I, depending on the presence or absence of hippocampal sclerosis (Fauser et al., 2004; Krsek et al., 2009; Tassi et al., 2010).

The purpose of our present study was to microscopically assess agreement and reproducibility levels of FCD variants specified in the 2011 ILAE classification system. We adopted our experimental design to a previously published study from Chamberlain et al. (2009), who addressed interobserver and intraobserver reliabilities for Palmini’s FCD classification (Palmini et al., 2004). A major difference in our study protocol was, however, the ability to distribute fully digitalized slides of routine and immunohistochemically stained specimens among a large and international group of neuropathologists by using an Internet-based virtual slide review platform. This system may also serve as an educational tool in the future, as we accomplished reliable concordance for the histopathologic diagnosis of epilepsy surgery specimens.

**Materials and Methods**

Twenty-two cases have been selected by two neuropathologists from the European Epilepsy Brain Bank (IB and RC). They were considered to comprise a broad spectrum of histopathologic subtypes and cytoarchitectural abnormalities defined by the ILAE classification system (Table 1).
Three surgical control specimens from patients without epilepsy were used as controls. All tissue specimens were fixed overnight in 4% formaldehyde and routinely processed in liquid paraffin according to standardized histopathology protocols. Sections were cut at 4 μm with a microtome (Microm, Heidelberg, Germany), and mounted on positively charged slides (Menzel, Braunschweig, Germany). Hematoxylin and eosin (H&E) stainings and histochemical reactions (Nissl-Luxol-Fast-Blue, Prussian-Blue) were performed from one representative tissue sample of each surgical case and fully digitalized using the dotSlide Virtual Slide System (Olympus, Tokyo, Japan) equipped with a 20× microscope objective. In addition, immunohistochemical stainings using antibodies directed against glial fibrillary acidic protein (GFAP, mouse monoclonal; Dako, Glostrup, Denmark), microtubule-associated protein 2 (MAP2, courtesy of Dr. Riederer), neurofilament protein (SMI32, mouse monoclonal; Covance, Emeryville, CA, U.S.A.), neuronal nuclear antigen (NeuN, mouse monoclonal; Merck Millipore, Billerica, MA, U.S.A.), intermediate filament Vimentin (mouse monoclonal; Dako), proliferation marker Ki67 (rabbit monoclonal; Thermo, Fremont, CA, U.S.A.), metabolic enzyme IDH-1 (mouse monoclonal; Dianova, Hamburg, Germany), or CD34 (mouse monoclonal; Dako) were performed with a semiautomated staining apparatus (see Table S1; Ventana Benchmark, Roche Diagnostics, Mannheim, Germany). Short summaries of clinical data including gender, age at surgery, seizure onset, localization, and side of resection were provided for each case (Table S1). There was no access to preoperative imaging or imaging reports.

For case evaluation, 10 experienced neuropathologists from six different countries (England, Germany, Italy, Japan, The Netherlands, U.S.A.) gained online access to the virtual slide system Digital Slidebox 4.5 (Slidepath; Leica Microsystems, Dublin, Ireland). Most of these reviewers were originally involved in the ILAE classification proposal and were asked to classify the cases within a 28-day period using only the published 2011 ILAE classification system and supporting online material. All diagnostic reports were submitted and retrieved from the Digital Slidebox system. Nine colleagues submitted their reports within the given time limit. None of the raters had access to results of other reviewers. The same nine participants re-reviewed the slide series after a 3-month interval. The website was not accessible during the interim period. The cases were provided in different order of appearance at the second evaluation round. In a third evaluation round, an international group of 30 neuropathologists with different levels of experience in epilepsy surgery were invited to evaluate the same series of cases. Levels of experience were defined by the number of epilepsy surgery cases reviewed at their local department in 2010. Twenty-one colleagues responded to the survey and completed their review within the 28-day period. Seven neuropathologists reported a level of experience above 40 cases/year (level A), eight neuropathologists had access to 10–40 cases/year (level B), and six neuropathologists reviewed <10 cases/year (level C).

Personalized results were visible and statistically analyzed only by the system administrator (OJdB), who is a senior assistant professor at the Pathology Department of Amsterdam neither experienced in epilepsy surgery nor enrolled in this survey or any other epilepsy-related scientific study. Interobserver agreement was calculated by κ coefficient analysis. The κ coefficient was also used to determine intraobserver reproducibility (Sim & Wright, 2005). Kappa values are always less than or equal to 1. In our study κ was interpreted as follows: <0.2, poor agreement; 0.2–<0.4, fair agreement; 0.4–<0.6, moderate agreement; 0.6–<0.8, good agreement; 0.8–1.0, very good agreement.

### Results

**Interobserver and intraobserver agreement in the first and second evaluation rounds**

Overall interobserver agreement at first review was good, with a calculated mean κ value of 0.6360. Agreement levels

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**Table 1. Clinicopathologic types of focal cortical dysplasias according to the ILAE classification system**

<table>
<thead>
<tr>
<th>FCD Type I</th>
<th>Type Ia</th>
<th>Type Ib</th>
<th>Type Ic</th>
</tr>
</thead>
<tbody>
<tr>
<td>(isolated)</td>
<td>FCD with abnormal radial microcolumns</td>
<td>FCD with abnormal horizontal cortical lamination</td>
<td>FCD with abnormal vertical and horizontal cortical lamination</td>
</tr>
<tr>
<td>FCD Type II</td>
<td>Type IIa</td>
<td>Type IIb</td>
<td></td>
</tr>
<tr>
<td>(isolated)</td>
<td>FCD with dysmorphic neurons</td>
<td>FCD with dysmorphic neurons and balloon cells</td>
<td></td>
</tr>
<tr>
<td>FCD Type III</td>
<td>Type IIIa</td>
<td>Type IIb</td>
<td>Type IIIc</td>
</tr>
<tr>
<td>(associated with principal lesion)</td>
<td>Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis</td>
<td>Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor</td>
<td>Cortical lamination abnormalities adjacent to another abnormality</td>
</tr>
</tbody>
</table>

The ILAE classification of focal cortical dysplasias defines isolated forms (FCD types I and II) and cortical dyslamination associated with a principal lesion (FCD type III). Modified from (Blumcke, Thom, Aronica, Armstrong, Vinters, Palmini, Jacques, Avanzini, Barkovich, Battaglia, Becker, Cepeda, Cendes, Colombo, Crino, Cross, Delalande, Dubeau, Duncan, Guerrini, Kahane, Mather, Najm, Ozkara, Raybaud, Represa, Roper, Salamon, Schulze-Bonhage, Tassi, Vezzani and Spreafico, 2011).
Intraobserver reliability was high and reached a $\kappa$ value of 0.7824. Four of nine neuropathologists showed very good and three good agreement, and there were only two raters with moderate reproducibility. Poor or fair intraobserver agreement was not encountered (Table 3). At reevaluation, least frequent changes were observed for the diagnosis of FCD type IIa/b (2.2% of 225 original diagnoses), whereas FCD type III diagnoses provoked most frequent changes (13.7%; Table 4).

Interobserver agreement in a third evaluation round

Agreement between our international group of 21 neuropathologists was moderate, presenting a $\kappa$ value of 0.4060, ranging from only 0.1509 for the diagnosis of FCD type Ic to very good for the diagnosis of FCD type IIb (0.8045; Table 2). Of interest, $\kappa$ values varied with experience levels, with highest agreement observed in the group of neuropathologists evaluating $>40$ cases per year (level A $\kappa = 0.5056$) to fair agreement in groups with lower expertise (0.3884 for level B and 0.3265 for level C; Table 2). Concordance was observed overall in 88% of cases (22/25; Table S7) including four cases in which diagnoses differed between the first and second evaluation rounds (case 5: no FCD vs FCD type IIIa, case 18: no FCD vs FCD type IIIa, case 21: no FCD vs FCD type IIIb, and case 25: no FCD vs FCD type IIIb; see Table S6). Level A raters showed agreement in 98% of cases (22/25) compared to our first and second round expert reviewers (cases 5, 16, and 25). Concordance was achieved in 64% of cases (16/25) at level B, and in 52% of cases (13/25) at level C, respectively.

Use of additional immunostaining

Our raters judged NeuN as the most valuable immunostaining for the differentiation of FCDs. This applied in particular to the differential diagnosis of FCD type I as well as FCD type III variants. Cytoarchitectural abnormalities, that is, dysmorphic neurons and balloon cells, were reliably detected using either SMI32 or vimentin stainings. This issue has also been acknowledged by the majority of raters, in particular to differentiate between FCD types IIa and IIb (Table S2).

Discussion

Our present study revealed good agreement and good reproducibility for neuropathologic evaluation of FCD categories using the 2011 ILAE consensus classification. Our analysis further supports the concept of particular clinicopathologic FCD subtypes, that is, FCD types IIa and IIb, which should always be identified by routine neuropathologic evaluation, if a surgical specimen is sufficiently large. On the other hand, less well-specified FCD variants remain challenging also for histopathologic assessment and will require additional laboratory expertise and training (i.e., FCD type Ic). This assumption is supported by our survey of 21 international neuropathologists with different levels of experience.

Table 2. Interobserver agreement in the first, second, and third evaluation rounds per FCD types ($\kappa$ values)

<table>
<thead>
<tr>
<th>Round</th>
<th>FCD Ia</th>
<th>FCD Ib</th>
<th>FCD Ic</th>
<th>FCD IIa</th>
<th>FCD IIb</th>
<th>FCD IIIa</th>
<th>FCD IIIb</th>
<th>FCD IIIc</th>
<th>FCD IIId</th>
<th>No FCD</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.4821</td>
<td>0.3877</td>
<td>0.1319</td>
<td>1.0000</td>
<td>1.0000</td>
<td>0.8316</td>
<td>0.4869</td>
<td>0.7685</td>
<td>0.6082</td>
<td>0.3746</td>
<td>0.6360</td>
</tr>
<tr>
<td>2</td>
<td>0.7084</td>
<td>0.4287</td>
<td>-0.004*</td>
<td>1.0000</td>
<td>0.9565</td>
<td>0.7862</td>
<td>0.5113</td>
<td>0.6435</td>
<td>0.5465</td>
<td>0.4164</td>
<td>0.6532</td>
</tr>
<tr>
<td>3T</td>
<td>0.3252</td>
<td>0.1917</td>
<td>0.1509</td>
<td>0.4239</td>
<td>0.8045</td>
<td>0.5822</td>
<td>0.4407</td>
<td>0.6109</td>
<td>0.1800</td>
<td>0.2409</td>
<td>0.4060</td>
</tr>
<tr>
<td>3A</td>
<td>0.4220</td>
<td>0.4323</td>
<td>0.3438</td>
<td>0.5252</td>
<td>0.7428</td>
<td>0.7199</td>
<td>0.6401</td>
<td>0.7033</td>
<td>0.2951</td>
<td>0.2606</td>
<td>0.5056</td>
</tr>
<tr>
<td>3B</td>
<td>0.3185</td>
<td>0.1071</td>
<td>0.1608</td>
<td>0.4311</td>
<td>0.8555</td>
<td>0.5063</td>
<td>0.4451</td>
<td>0.5981</td>
<td>0.0517</td>
<td>0.2586</td>
<td>0.3884</td>
</tr>
<tr>
<td>3C</td>
<td>0.3763</td>
<td>0.0778</td>
<td>0.2137</td>
<td>0.3307</td>
<td>0.7136</td>
<td>0.4911</td>
<td>0.2171</td>
<td>0.4718</td>
<td>0.1955</td>
<td>0.1270</td>
<td>0.3265</td>
</tr>
</tbody>
</table>

3T, summary of third evaluation round including all 21 neuropathologists; 3A, neuropathologists with level A access to >40 epilepsy surgery cases/year; 3B, neuropathologists reviewing 10–40 cases/year; 3C, neuropathologists seeing <10 cases/year.

Kappa values were scored as follows: <0.2, poor agreement; 0.2–<0.4, fair agreement (yellow boxes); 0.4–<0.6, moderate agreement (purple boxes); 0.6–<0.8, good agreement (green boxes); 0.8–1.0, very good agreement (blue boxes).

*Kappa values can be negative in rare situations indicating that the observers agreed less than expected by chance.
and access to epilepsy surgery. We would like to propose two future strategies to enhance consensus and reliability levels even for difficult-to-diagnose FCD subtypes. Semiquantitative histopathologic measurements of aberrant cellular profiles, cortical layer abnormalities, and white matter changes were not specified in the ILAE classification system and should be made available for routine microscopic workup, as recently proposed by Muhlebner et al. (2012). On the other hand, virtual slide reviewing systems similar to that used in our study may be helpful to disseminate knowledge and provide an ILAE FCD teaching platform.

A similar study design was reported previously by Chamberlain et al. (2009) to approach interobserver and intraobserver reliability of the Palmini classification of FCDs. They included a group of eight Northern American neuropathologists experienced in epilepsy surgery and evaluated a series of glass slides obtained from 26 surgical epilepsy samples. This study reported moderate interobserver agreement with a $\kappa$ value of 0.4968, and moderate to very good intraobserver reproducibility levels ($\kappa = 0.4654–0.8504$). Greatest concordance was accounted for in FCD types IIa/b, whereas the classification of Palmini’s FCD types Ia and Ib remained challenging. Mild MCDs (mMCDs) were also included in their trial but least reproducible (Chamberlain et al., 2009). Our survey reached a higher $\kappa$ value of 0.6532 for interobserver consensus among an international group of nine neuropathologists. However, we should not directly compare both studies, as our study design included substantial differences: (1) we had access to additional histochemical and immunohistochemical stainings as well as inclusion of a larger spectrum of FCD subtypes; (2) our study did not consider mMCDs; (3) we used a virtual slide review system and were able to provide a large number of slides (188) for histologic evaluation; (4) with use of this technique we could reach an international group of participating neuropathologists from all different continents and with different levels of experience; And (5) all raters had to review identical sections. Our study design also had disadvantages, as some participants used a telepathology reviewing system for the first time. We cannot rule out the possibility, therefore, that all reported diagnoses were given correctly as each rater had to click on predefined answers on a computer button instead of writing down the diagnosis in letters. We do also not know if differences occurred in the perception of histology slides using a two-dimensional computer screen compared to three-dimensional live microscopy. Finally, the ILAE consensus classification relies on clinicopathologic patterns, taking into account not only histopathologic criteria but also defining of clinical FCD subtypes by EEG findings and neuroimaging, not provided in this study.

FCD type II reached a very good or good agreement level for both IIa and IIb subtypes. Since its first description by
Taylor et al. in the early 1970s, FCD type II was consistently recognized and huge advances were achieved to identify the subtypes in routine clinical workup or presurgical monitoring protocols (Sisodiya et al., 2009). FCD types IIa and IIb should be regarded, therefore, as specific clinico-pathologic entities presenting with a well-defined set of clinical, electrophysiologic, and imaging features (Wagner et al., 2011). Use of well-characterized tissue samples will allow also seminal progress in understanding pathogenic hallmarks and epileptogenicity. Well-defined histopathologic patterns remain, therefore, instrumental for defining this peculiar FCD category and this is well reflected by an almost perfect concordance using the 2011 ILAE consensus classification (Tables 2 and 4).

The ILAE consensus classification specifies three FCD type I subtypes, according to the occurrence of radial microcolumns (FCD type Ia), laminar alterations (FCD type Ib), or a combination of both, that is, FCD type Ic. Good agreement was observed for the diagnosis of FCD type Ia and moderate agreement for type Ib, whereas no agreement was found for the diagnosis of type Ic. The difficulty of confining this latter subtype may be due to the fact that it comprises different degrees of histopathological changes enclosed in FCD Type Ia and Type Ib as well as the lack of published series of this subtype. However, when pooling all three FCD type I subtypes into one category, moderate to almost good agreement can be envisaged.

FCD type III has been newly introduced into the ILAE consensus classification to differentiate between associated and isolated FCDs. Very good agreement was achieved for the diagnosis of FCD type IIIa (associated with hippocampal sclerosis), which is the most frequently reported FCD subtype (Blumcke et al., 2009). Of interest, FCD type IIIc and type IIIId also reached good agreement levels, whereas the concordance for FCD type IIIb, defined by cortical laminar abnormalities associated with neoplasia, was moderate. Difficulties resulted in distinguishing this subtype from no-FCD. Of note, three of five cases in which FCD type IIIb was considered were represented by patients with malignant gliomas but no history of epilepsy, which were used in our series as control specimens. This implies that tumor infiltration and altered cortical structures have been well recognized. However, the ILAE FCD classification proposed to exclude FCD variants in cortical areas with evident tumor cell infiltration.

In a third evaluation round we aimed to test the reliability of diagnostic criteria specified in the ILAE consensus report as well as to test the applicability of a virtual slide reviewing system in a group of international neuropathologists with different levels of experience and access to epilepsy surgery specimens. There was moderate overall agreement ranging from poor to very good concordance levels. Evaluation based on experience levels revealed moderate agreement in the group of neuropathologists with highest expertise. These values declined with lower access to epilepsy surgery specimens. Most skilled raters achieved 92% agreement, which was almost at the same level with our expert reviewers. Concordance was achieved in 64% of cases at level B and 52% of cases at level C, respectively. There were four cases in which expert agreement differed from the third evaluation round agreement. Here, the discrepancies consisted of the discrimination between FCD and no-FCD, with less skilled raters rendering the diagnosis of a cortical
malformation more often. Best agreement was achieved again for the diagnosis of FCD types IIa and IIb.

Our results suggested that the revised ILAE definition of FCD histopathology patterns improved operational procedures in the diagnosis of FCDs. Microscopic assessment of FCD specimens remains, however, a challenging topic in surgical neuropathology and will require sustained experience, practice, and teaching as well as advanced immunohistochemical procedures. Indeed, use of additional immunostains was most helpful for the differential diagnosis (see Table S2) of FCD type I and III variants. We anticipate, however, the restricted availability of such advanced laboratory protocols in many countries with limited financial and technical resources. On the other hand, epilepsy surgery programs were usually established at specialized clinical centers and our results support the notion that histopathology laboratories should also be adapted to this level of expertise. Second opinion consultation at neuropathology reference centers may also represent an option to accomplish and provide expert diagnostic work-up.

Although rater agreement for the new ILAE classification was good, histopathologic analysis will still not be able to unravel the epileptogenic nature of a given structural brain lesion. This aspect has already been discussed in the original classification paper and will need further studies. This applies in particular to the new ILAE FCD type IIIa category associated with hippocampal sclerosis. Presented data

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**Table 3. Intraobserver reproducibility in the ILAE classification system**

<table>
<thead>
<tr>
<th>NP</th>
<th>Unchanged diagnoses</th>
<th>Changed diagnoses on reevaluation</th>
<th>( \kappa )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/25</td>
<td>3/25</td>
<td>0.8575</td>
</tr>
<tr>
<td>2</td>
<td>16/25</td>
<td>9/25</td>
<td>0.5849</td>
</tr>
<tr>
<td>3</td>
<td>19/25</td>
<td>6/25</td>
<td>0.7180</td>
</tr>
<tr>
<td>4</td>
<td>20/25</td>
<td>5/25</td>
<td>0.7657</td>
</tr>
<tr>
<td>5</td>
<td>23/25</td>
<td>2/25</td>
<td>0.8899</td>
</tr>
<tr>
<td>6</td>
<td>19/25</td>
<td>6/25</td>
<td>0.7268</td>
</tr>
<tr>
<td>7</td>
<td>25/25</td>
<td>0/25</td>
<td>1.0000</td>
</tr>
<tr>
<td>8</td>
<td>14/25</td>
<td>11/25</td>
<td>0.4991</td>
</tr>
<tr>
<td>9</td>
<td>25/25</td>
<td>0/25</td>
<td>1.0000</td>
</tr>
<tr>
<td>Summary</td>
<td>183/225</td>
<td>42/225</td>
<td>0.7824 (mean)</td>
</tr>
</tbody>
</table>

NP, neuropathologist.
Kappa values were interpreted as follows: <0.2, poor agreement; 0.2–<0.4, fair agreement; 0.4–<0.6, moderate agreement; 0.6–<0.8, good agreement; 0.8–1.0, very good agreement.

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**Table 4. Intraobserver variation**

<table>
<thead>
<tr>
<th>Re-evaluation Diagnoses</th>
<th>No FCD (55)</th>
<th>FCD Type I (39)</th>
<th>FCD Type II (44)</th>
<th>FCD Type III (87)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Diagnoses (n=225)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No FCD (46)</td>
<td>42</td>
<td>2</td>
<td>2</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>FCD Type I (39)</td>
<td>3</td>
<td>34</td>
<td>2</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>FCD Type II (45)</td>
<td></td>
<td></td>
<td>44</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>FCD Type III (95)</td>
<td>10</td>
<td>3</td>
<td>82</td>
<td>13.7</td>
<td></td>
</tr>
</tbody>
</table>

Bolded values: diagnoses unchanged at reevaluation (202/225). Dashed boxes changed diagnoses at reevaluation (23/225).
have been most controversial, as both populations of patients with mesial temporal lobe epilepsy and hippocampal sclerosis with/without associated FCD showed similar response to outcome (Tassi et al., 2010).

**Disclosure**

The authors have no conflict of interest to declare. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**References**


**Supporting Information**

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

**Table S1.** Clinical data of studied cases and available stainings.

**Table S2.** Evaluation of useful immunohistochemical stainings.

**Table S3.** Summary of 25 cases classified by nine neuro-pathologists in the first and second evaluation rounds.

**Table S4.** Interobserver agreement in the first, second, and third evaluation rounds per FCD type groups (K values).

**Table S5.** Agreement per FCD type in the first and second evaluation rounds.

**Table S6.** Classification of 25 cases by 21 neuropathologists in the third evaluation round.

**Table S7.** Agreement per FCD type in the third evaluation round.

**Table S8.** Interobserver agreement in different evaluation rounds with pooled ratings for FCD types I and III.

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