Original article

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A distinct variant of focal cortical dysplasia type I characterised by magnetic resonance imaging and neuropathological examination in children with severe epilepsies

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ABSTRACT – Focal Cortical Dysplasias (FCDs) present with a large clinicopathological spectrum. FCDs are believed to relate directly to an epileptogenic condition, although seizure control by surgical resection is variable. This applies in particular to young children with multilobar FCDs, suffering from severe epilepsies and psychomotor retardation. Herein, we performed a comparative analysis of presurgically available data and microscopic inspection of resected cortical specimens to further characterise the pathomorphological spectrum of FCD. Multilobar resection procedures were performed in a consecutive series of 18 young children (mean 7.6 years) with severe pharmaco-resistant epilepsies following extensive presurgical surface-/invasive video-EEG monitoring intraoperative electro-corticography (iECoG), as well as high resolution MRI. In all cases, systematic neuropathological examination of surgical specimens was performed with respect to architectural abnormalities and cell density measurements. These histomorphological data were compared with volumetric MRI analysis. Histopathological examination revealed increased neuronal densities correlating with decreased cortical thickness and abundance of neuronal microcolumns in all cases. Intriguingly, the affected cerebral hemisphere was significantly smaller, relative to the non-epileptogenic contralateral side, in 16 children of our patient series. In conclusion, hypoplastic neocortex and columnar architectural disorganisation point to compromised cortical development, and appear as distinct FCD I subtype in children suffering from severe epilepsies and psychomotor retardation.

Key words: malformation, development, seizures, neuropathology, MRI, focal cortical dysplasia

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The term "focal cortical dysplasia" was coined by D. Taylor and co-workers in 1971, describing a peculiar histopathological finding with cortical disorganisation, large bizarre neurons and balloon cells in a series of ten surgical epilepsy patients (Taylor *et al.*, 1971). Since then, the term FCD has been widely introduced to include a large spectrum of alterations comprising cortical dyslamination and cytoarchitectural lesions (Palmini *et al.*, 2004). FCDs occur isolated in adults or children, or can be detected adjacent to hippocampal sclerosis, glio-neuronal tumours, vascular malformations or perinatal brain damage (Blümcke *et al.*, 2009).

At present, FCDs should be histopathologically distinguished as type I or II (Palmini *et al.*, 2004). FCD type IA refers to architectural disturbances of cortical lamination, and FCD type IB includes cytoarchitectural abnormalities. FCD type IIA is characterised by the presence of disoriented and abnormally large dysmorphic neurons, whereas the histopathological diagnosis of FCD type IIB also includes the presence of balloon cells. FCDs can be located in any part of the cortex. They have variable size and location, and may also affect multiple lobes (Hildebrandt *et al.*, 2005; Krsek *et al.*, 2009).

Seizure onset starts usually during childhood and seizures very often progress to become 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 frequencies (Chassoux *et al.*, 2000; Palmini *et al.*, 1995; Tassi *et al.*, 2002). However, there is considerable controversy over the reported clinical presentation of patients with FCD type I, which is most likely due to the difficulty of accurate classification (Blümcke *et al.*, 2009; Chamberlain *et al.*, 2009). This applies also to the neuroimaging characteristics of FCDs, in which patients diagnosed with the same Palmini FCD subtype present with different imaging findings (Colombo *et al.*, 2009; Krsek *et al.*, 2008; Lerner *et al.*, 2009). Whereas the majority of published FCD type I series are also reported to suffer from hippocampal sclerosis (Fauser and Schulze-Bonhage, 2006; Tassi *et al.*, 2002), isolated FCDs are detected mostly in children with refractory severe epilepsies involving multiple lobes and mental retardation (Krsek *et al.*, 2008; Krsek *et al.*, 2009). Abundant neuronal microcolumns, smaller neuronal perikarya and significantly increased numbers of ectopic white matter neurons are reported to represent histopathological hallmarks in surgical specimens obtained from these children (Hildebrandt *et al.*, 2005). MRI abnormalities were reported to be only moderate, *e.g.* blurred grey-white matter boundaries or slightly increased T2-signals.

In the present study, we performed MRI volumetric measurements of affected vs. non-affected hemispheres, as well as anatomically defined cortical lobes, in a series of 18 children with early seizure onset. Correlation with microscopically determined architectural abnormalities (*i.e.* cortical thickness, neuronal cell density and microcolumns) in surgical specimens obtained from the same series of patients was investigated to further characterise this distinct FCD variant.

Methods

Clinical examination

Eighteen children (age 2 to 18 years, mean 7.6 ± 4.9 years) with epilepsy and histopathologically confirmed FCD type I were included in this study. There was a nearly equal distribution of gender (10 males and 8 females) and equal distribution of patients who were operated on either side; nine on the left and nine on the right side *(table 1)*. Extensive presurgical evaluation was conducted for each patient at the Epilepsy Center for Children and Adolescents in Vogtareuth (Germany), including preoperative video-EEG-monitoring, high resolution MRI, 18FDG-PET-imaging, and neuropsychological examination. Prolonged video-EEG monitoring was helpful to identify ictal onset and maximum spike areas. Intraoperative electrocorticography (iECoG) was routinely performed at the end of each operation to confirm the epileptogenic area was completely resected. The majority of patients received multilobar resections. In 15 cases, the hippocampus was removed due to widespread EEG discharges throughout the temporal lobe and mesial structures. However, only one patient displayed mesial temporal sclerosis (MTS) following neuropathological examination. Neuropsychological protocols were based on standardised utilities depending on age and intellectual capacities and performed for all children. None of the children reached average or high intelligence levels (defined as > 99; Wechsler Intelligence Scale for Children HAWIK-III). Furthermore, Vineland Maladaptive Behavior Scales were available for 11 children, and revealed normal values only in two patients. Standardised follow-up evaluations were performed six months postoperatively and then annually. Surgical outcome was classified according to Engel's classification (Engel *et al.*, 1993): (I) completely seizure-free, auras only or atypical early postoperative seizures only; (II) ≥ 90% seizure reduction or nocturnal seizures only; (III) ≥ 75% seizure reduction; and (IV) < 75% seizure reduction. Seizure outcome at the last follow-up visit was given as a general outcome overview. The mean follow-up period was 4.39 years (ranging from 2 to 6 years).

MR recording and volumetry

High resolution, 1,5 Tesla magnetic resonance imaging (MRI, Siemens Sonata/Vision) was performed for all patients. T_1 3D (MPRAGE) with 1 mm partitions and 2-3 mm transverse and coronal FLAIR sequences were obtained. Additional scanning performed in all patients

Table 1. Clinical data of patients with FCD type I included in this study (n = 18).

ID	Age OP (yrs)	Age Onset (yrs)	Sex	Side	Resected area	MTS	Volume path	Volume contra-lateral	Outcome
1	2.5	1.0	m	L	TL, Occ, HC	no MTS	513.08	509.02	II
2	2.6	0.9	m	L	TL, Occ, HC	MTS	304.35	327.8	I
3	2.6	0.8	f	L	TL, Occ, HC	no MTS	502.9	682.88	I
4	3.3	1.0	f	L	TL, Occ, FL, HC	no MTS	418.73	419.92	IV
5	4.5	0.5	m	R	TL, Occ, FL, HC	no MTS	814.41	850.55	III
6	4.6	0.5	m	R	TL, Occ, HC	no MTS	540.33	542.64	III
7	4.7	0.9	f	L	TL, Occ, HC	no MTS	800.99	840.34	III
8	6.3	4.0	m	R	TL, Occ, HC	no MTS	802.97	839.97	II
9	6.3	1.7	m	L	TL, FL, HC	nd	830.46	890.05	IV
10	6.8	0.3	f	L	TL, Occ, HC	no MTS	515.55	529.57	IV
11	11.5	0.3	m	R	FL, TL, HC	no MTS	447.97	509.36	II
12	2.6	1.7	m	L	TL, Occ, HC	no MTS	435.93	443.53	III
13	14.8	10.0	f	R	TL, Occ, HC	no MTS	855.61	842.45	IV
14	15	2.0	m	R	FL	nd	916.98	915.52	IV
15	18.8	0.8	f	R	FL	nd	750.37	919.7	III
16	11.8	1.5	f	R	Occ	nd	577.94	688.46	III
17	6.4	3.3	m	L	TL, Occ, HC	no MTS	504.41	517.5	I
18	8	1.1	f	R	TL, Occ, HC	no MTS	521.4	538.,81	II

ID: identification number; Age OP: age at operation; m: male; f: female; Side: side of resection; L: left side; R: right side; TL: temporal lobe; FL: frontal lobe; Occ: occipital lobe; HC: hippocampus; MTS: mesial temporal sclerosis; nd: not determined- no surgical hippocampus specimen available or severe hippocampus tissue fragmentation (patient 9); Volume path/Volume contralateral: MRI volume of affected or contralateral hemisphere in cm^3; Outcome: seizure outcome classified according to Engel I to IV.

included 1 mm continuous axial 2D T_2 turbo spin echo images with a minimum in-plane resolution of 292 x 512 and a maximum size of field-of-view of 23 cm. Volumetric measurements were performed by manual segmentation of each cortical lobe and hemisphere using MPRAGE data sets or 2D T_2 turbo spin echo images *(figure 1)*.

Tissue preparation and neuropathological analysis

Multilobar epileptogenicity was identified for the majority of patients using surface EEG *(table 1)*. The characterisation of the epileptogenic area resulted in tailored resection modalities in all patients. En bloc resected specimens were available in all cases. When multilobar resections were performed, representative tissue samples from

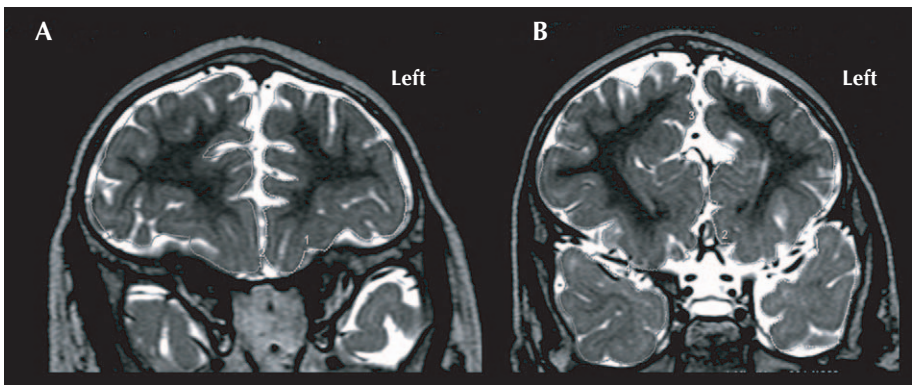

Figure 1. Examples of serial high resolution MRI scans of patient 3, who suffered from intractable epilepsy originating from the left hemisphere. Histopathological examination confirmed severe architectural abnormalities, *i.e.* FCD type I (see *table 1* and *figure 2*). Areas were calculated following manual segmentation of temporal and frontal lobes (coloured dots were superimposed to better visualize quantified areas).
A) Right *vs* left frontal = 14.89-12.34 cm^2.
B) Right *vs* left frontal = 19.80-14.96 cm^2 and right *vs* left temporal = 6.99-6.30 cm^2.

every circumscribable lobe were separately investigated. All tissue specimens were microscopically examined by the Neuropathological Reference Center for Epilepsy Surgery (Blümcke *et al.*, 2007). Adjacent tissue obtained from nine age-matched children (age 2 to 16 years, mean 9.0 ± 4.7 years), who underwent tumour resection of low-grade epilepsy-associated tumours such as gangliogliomas (WHO I) or dysembryoplastic neuroepithelial tumours (WHO I) without evidence for FCD, served as control.

Biopsy samples were fixed overnight in 4% formalin and routinely processed in liquid paraffin. All specimens were cut at 4 µm with a microtome (Microm, Heidelberg), stretched in water at 40°C and mounted on slides coated with silane (Langenbrinck; Emmendingen, Germany). The slides were air-dried in an incubator at 37°C overnight, deparaffinised in descending alcohol concentration and pretreated in a microwave (only for immunohistochemical reactions). Haematoxylin and eosin (H&E) staining was used for all specimens.

Immunohistochemistry

Immunohistochemical reactions were performed using an automated staining apparatus and streptavidin-biotin method (Ventana; Strasbourg, France), 3,3′-diaminobenzidine as chromogen and haematoxylin counterstaining. Neurons were visualized using monoclonal antibodies directed against the neuronal core antigen NeuN (mAB 377 diluted 1:1000, obtained from Chemicon, Temecula, USA).

Semi-quantitative analysis

Paraffin-embedded sections from each specified cortical lobe were immunohistochemically stained with antibodies against NeuN to identify neurons. All measurements were performed in gyri and sulci, in which the pial surface paralleled the grey-white matter border and subarachnoidal blood vessels entered perpendicularly into the neocortex. Adjacent micrographs were taken at 40 x magnification from cortical lamina I to the white matter and comprised an overview figure of the entire area. A total of 75 overview micrographs (30 from the temporal lobe, 31 from the occipital lobe and 14 from the frontal lobe) were available for semi-quantitative investigation. In addition, 20 age-matched specimens (ten from the temporal, four from the occipital and six from the occipital lobe), adjacent to tumour resection and without evidence of FCD, served as controls.

Cortical thickness was defined as the distance between the pial surface and the white matter border below lamina 6 (in µm). Although architectural abnormalities were evident in all epilepsy specimens, laminar borders could still be recognized. The border between L1 and L2 was always distinguishable. A granular appearance of neurons in layers 2 and 4 was also helpful. However, the distinction between L5 and L6 was not always easy to determine. In those cases, we assumed the border at half distance towards the white matter. NeuN immunoreactive neurons presenting with a visible nucleus were depicted on the computer screen and assigned to the respective layers. Neuron cell densities were calculated per mm^2 for each cortical lamina as well as the entire neocortex following segmentation of the respective cortical field by a microcomputer imaging system (AnalySIS imaging software and ColorView II CCD camera; Stuttgart, Germany) equipped with a BX51 microscope (Olympus, Japan). Of note is the fact that paraffin-embedded sections were processed at a thickness of 4 µm, allowing only two-dimensional analysis.

Microcolumns were defined according to our previous description with more than eight neurons (in cortical layer III) oriented in vertical direction. The visual field was divided into vertical segments of 60 µm width (Hildebrandt *et al.*, 2005). All neurons within one row or crossing the left border were captured on the computer screen. The numbers of microcolumns (> eight neurons) were calculated as a percentage of the total number of measured segments from each immunohistological preparation (NeuN staining).

Statistical methods

Statistical evaluation was performed using the Statistical Package for the Social Sciences (SPSS+12). Correlations between neuronal density, cortical thickness, number of columns and MR volume were performed with Pearson's correlation coefficient. Inter-hemispheric comparisons were measured using the matched paired t-test (Wilcoxon signed rank test). Differences between temporal, occipital and frontal lobes were statistically compared using univariate analysis (ANOVA). P values < 0.05 were considered as significant.

Results

Volumetric analysis of cortical regions

Volumetric analysis was performed from T_1 3D MRI (MPRAGE) obtained from 18 patients with severe intractable epilepsies. The patient cohort showed a high inter-individual variability in hemispheric volume of the unaffected side (*table 1*) which correlated with age ($r = 0.560$; 2.5-18.8 years). Comparisons between MRI volume, gender or affected side revealed no statistical difference. A matched paired analysis between both hemispheres within individual patients unravelled a 6.1% mean volume deficit (range: - 1.6-26.4%) of the affected hemisphere ($p = 0.006$; *figure 2*). Volume differences between non-epileptic and affected sides were also calculated for temporal, occipital and frontal regions and reached a statistical level of significance for the temporal ($p = 0.0312$) and occipital lobe ($p = 0.0379$; *table 2*).

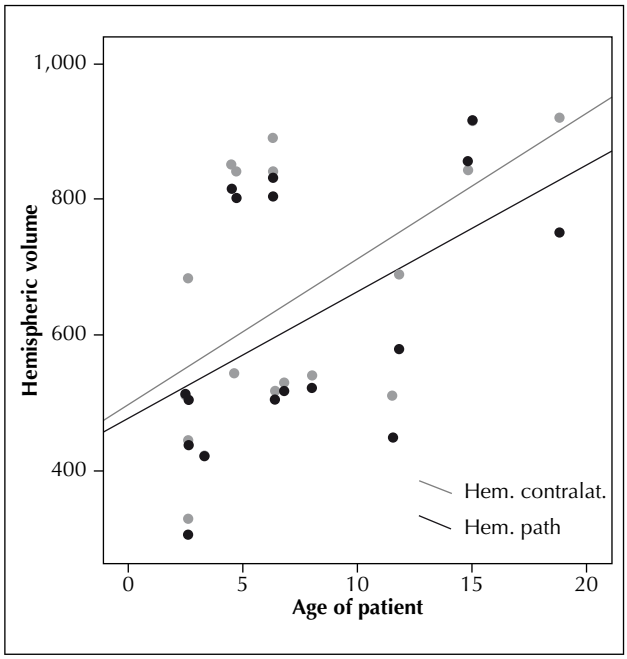

Figure 2. Correlation between age and hemispheric volume in young FCD patients. Manual segmentation of hemispheric volumes showing an age dependent increase of the contralateral, unaffected side (Hem. contralat.). A similar increase was observed for the epileptogenic hemisphere (Hem. path) in older patients ($p < 0.35$), although to a lesser extent. When both hemispheres were compared in individual patients, the epileptogenic hemisphere was significantly smaller ($p < 0.006$, paired T-test).

Table 2. Volumetric MRI analysis of FCD type I. The mean hemispheric volume as well as the volumes of the temporal lobe (TL) and occipital lobe were reduced on the pathological side of patients with FCD type I (n = 18).

	Mean volume (cm^3)	Standard deviation	p
Hem epileptogenic	629.0	190.8	
Hem normal	670.0	199.2	0.0047
TL epileptogenic	109.8	38.2	
TL normal	114.8	37.4	0.0312
FL epileptogenic	311.6	121.2	
FL normal	321.7	121.1	ns
Occ epileptogenic	115.2	34.5	
Occ normal	120.5	36.7	0.0379

Hem: hemisphere; FL: frontal lobe; Occ: occipital lobe; ns: not significant.

Neuropathological examination

Microscopic analysis of neocortical architecture was performed for all surgical specimens with FCD type I (n = 75) and age-matched controls (n = 20). For FCD type I the mean cortical thickness was 2,661.9 ± 431.7 µm with statistically significant differences between the occipital lobe (smallest; 2,467.1 ± 327.2 µm), frontal region (2,759.7 ± 341.2 µm) and temporal lobe (largest; 2,817.7 ± 492.3 µm; $p = 0,003$). However, cortical thickness was not different between patients with FCD type I and controls (2,749.3 ± 412.7 µm). In contrast, we observed regional differences of neuronal densities for FCD type I, with greatest values corresponding to the occipital lobe (450.7 ± 70.4 neurons per mm^2). Significantly lower cell densities were observed in the temporal (353.9 ± 62.9 neurons per mm^2) and frontal regions (331.2 ± 38.5 neurons per mm^2). These regional differences were not detected in control specimens ($p < 0.001$).

Neuronal microcolumns were observed in all surgical specimens *(figure 3)*. A "microcolumn" was defined as more than eight neurons aligned in vertical direction (Hildebrandt *et al.*, 2005), resembling ontogenetic columns described during normal cortical development (Rakic, 1988). They were most frequently observed in Layer 3 (which was also chosen as an area for quantitative measurement; the adjacent Layer 4 is often poorly defined). The same architectural arrangements were also occasionally present in age-matched control specimens (9% of vertical segments analysed). A statistically significant increase was observed for all surgical samples ($n = 75$) with a mean percentage of 32% ($p < 0.001$). There were regional differences in the occipital lobe (42%) compared to temporal (22%) and frontal regions (29%; $p < 0.001$). Further histopathological findings detected in the present series of surgical specimens included increased numbers of ectopic neurons in the white matter (Hildebrandt *et al.*, 2005) and enlarged perivascular spaces around white matter arterioles, *i.e.* spongiform angiopathy (Hildebrandt *et al.*, 2008). However, these latter features were also observed in other epilepsy-associated malformative or neoplastic lesions (Hildebrandt *et al.*, 2008).

Correlation analyses were performed between cortical thickness, abundance of microcolumns and neuronal cell densities for all surgical specimens with FCD type I ($n = 75$). A thinner cortex was shown to contain a significantly greater neuronal cell density ($r = - 0.556$, $p < 0.001$; *figure 4A*). The occurrence of microcolumns was also associated with increased neuronal cell densities ($r = 0.456$, $p = 0.002$; *figure 4B*). Our manual segmentation method did not allow us to specifically compare cortical and white matter volumes. As a consequence, we could not demonstrate correlation analyses with neuronal cell densities or cortical thickness measurements.

Discussion

High resolution brain imaging is mandatory for children with severe epilepsies in order to identify structural abnormalities (Barkovich *et al.*, 2005; Colombo *et al.*, 2009). Such abnormalities can be detected by MRI in up to

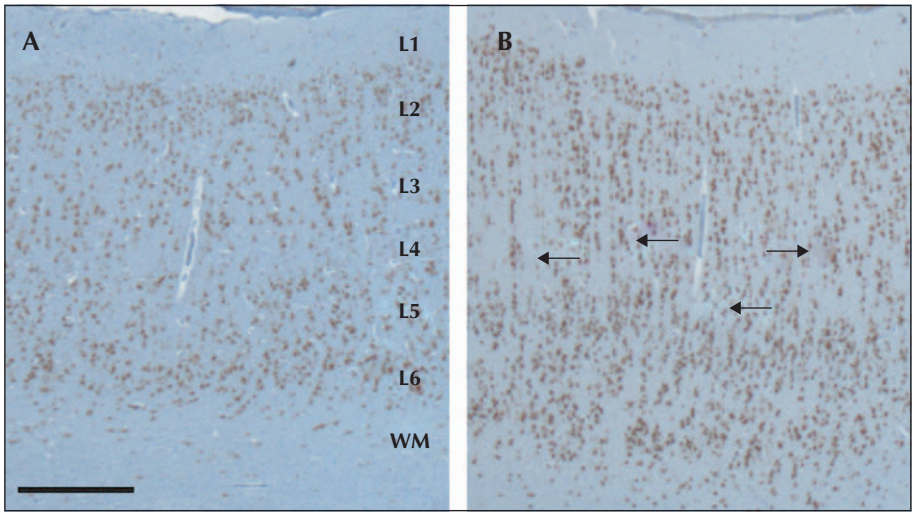

Figure 3. Neuropathological characteristics of FCD type I in children with severe epilepsy.
A) Characteristic cortical layering (L1-L6) in the human occipital lobe visualised by NeuN immunoreactivity. Scale bar = 500 µm.
B) Cortical specimen obtained from the occipital lobe of a 2.6 year old child with FCD type I. Cortical layers and border towards the white matter (WM) are less well demarcated.
Note the abundance of neuronal microcolumns and stratification, particular in layer 3 (arrows). Scale is the same as for (**A**).

80% of paediatric epilepsy surgery patients younger than three years of age (Krsek *et al.*, 2008; Krsek *et al.*, 2009). However, presurgical diagnosis of FCD type I remains challenging in children with epilepsy and additional morphometric parameters would be helpful (Blumcke *et al.*, 2009; Chamberlain *et al.*, 2009).
Volume deficits of the affected, relative to the non-affected, hemisphere were a frequent finding for the majority of our cohort of young patients ($p = 0.0047$). Reduced cortical volumes were identified for multiple lobes, *i.e.* temporal, frontal and occipital regions, respectively; those for the temporal and occipital lobes reached statistical significance. Recent MRI studies have also proposed an association with neocortical volume deficits in adult epilepsy patients suffering from hippocampal sclerosis (HS) (Briellmann *et al.*, 1998; Diehl *et al.*, 2004; Moran *et al.*, 2001; Seidenberg *et al.*, 2005). Extrahippocampal atrophy is reported not to be restricted to the temporal lobe in HS patients, and often involves the entire hemisphere (Briellmann *et al.*, 1998). It is of note that FCD type I can be histopathologically confirmed within the temporal lobe in many of these patients (Fauser and Schulze-Bonhage, 2006; Moran *et al.*, 2001; Tassi *et al.*, 2002; Tassi *et al.*, 2009; Thom *et al.*, 2009). Histopathology patterns are, however, distinct between both patient groups. Whereas HS associated FCDs present with horizontal abnormalities in cortical organisation, *i.e.* "supragranular layer and concomitant neuronal cell loss in layer 3" (Tassi *et al.*, 2002), also coined as "temporal lobe sclerosis" (Thom *et al.*, 2009), radially or vertically oriented abnormalities (microcolumns) have never been reported in adult HS patients.
The aetiology of FCD type I variants remains to be determined. Early exogenic lesions, such as hypoxia, infection during pregnancy or birth trauma may play a role (Marin-Padilla, 1999; Marin-Padilla *et al.*, 2002; Miller *et al.*, 1993; Sisodiya, 2004). In a *post mortem* study with infants who survived perinatally acquired encephalopathies, primarily undamaged cortical regions developed histopathological patterns reminiscent of cortical dysplasia (Marin-Padilla *et al.*, 2002). Chronic seizures were a clinical hallmark in many of these children indicating that loss of high order brain organisation is associated with increased seizure susceptibility. Frequent co-morbidity with mental and motor retardation in this group of young patients further points to progressive damage affecting multiple network systems and different cortical regions (Crino *et al.*, 2002; Holmes, 2004; Montenegro *et al.*, 2002; Sisodiya, 2004). Sustained seizure activity challenges the molecular machinery of neuronal networks during development as well as in the mature brain (Becker *et al.*, 2003; Crino and Becker, 2006), prompting aberrant synaptic connections as well as acquired expression patterns of voltage-gated ion channels which are potential target structures for increased epileptogenicity (Bernard *et al.*, 2004; Sutula, 2004). Yet, there is no hint for the existence of specific genetic abnormalities in FCD type I (Majores *et al.*, 2005), in contrast to recently reported mutations, polymorphisms and loss of heterozygosity in the TSC1 gene locus described for patients with FCD type IIB (Becker *et al.*, 2002).

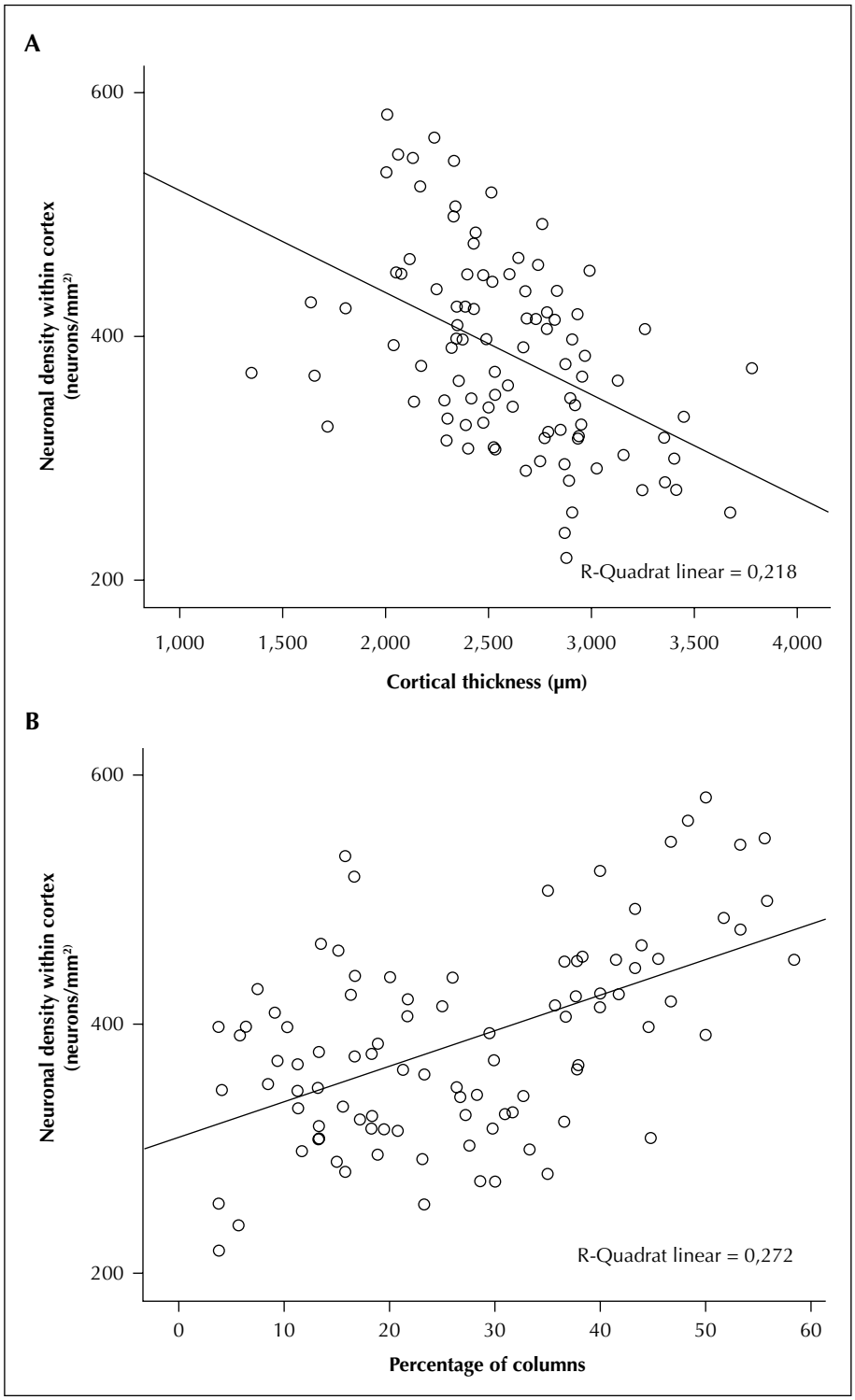

Figure 4. A) Correlation between cortical thickness and neuronal density in FCD type I. Neuronal cell densities were greater in small cortices ($r = -0.556$, $p < 0.0001$).
B) Correlation between neuronal density and microcolumns in FCD type I. A significant correlation occurred between neuronal cell densities and abundance of microcolumns in FCD type I ($r = 0.456$, $p = 0.002$).

Based on our series of 18 children suffering from severe epilepsy, our data identify hypoplastic epileptogenic hemispheres and "persistent" radial organisation of the affected neocortex. Microcolumnar neuronal cell patterns very much resemble the "radial unit lineage model of cortical neurogenesis" (Rakic, 2009), which should not be histologically visible at late postnatal stages in the human brain. The microcolumnar organisation points to a compromised cortical development as an underlying pathomechanism of this FCD variant. Whether this pattern also results from post-migrational events affecting the maturation of cortical networks remains to be clarified by systematic molecular analysis of affected brain tissue. We propose that this FCD variant should be separated from adult and/or associated FCD type I variants, previously reported to occur with other principal lesions, *i.e.* hippocampal sclerosis (Fauser and Schulze-Bonhage, 2006). □

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

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