

# Abnormal development of the human cerebral cortex: genetics, functional consequences and treatment options

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**Genetic studies have identified several of the genes associated with malformations of cortical development which might disrupt each of the main stages of cell proliferation and specification, neuronal migration and late cortical organization. The largest malformation groups, focal cortical dysplasia, heterotopia and polymicrogyria, express different perturbations of these stages and carry a variable propensity for lacking activation, preservation or reorganization of cortical function and for atypical cortical organization. Some patients have obvious neurological impairment, whereas others show unexpected deficits that are detectable only by screening. Drug-resistant epilepsy is frequent but might be amenable to surgical treatment. However, the epileptogenic zone might include remote cortical and sub-cortical regions. Completeness of resection, a key factor for successful surgery, might be difficult, especially in proximity to eloquent cortex. Surgical planning should be based on assessments of structural imaging and of the major functions relevant to the area in question in any such patient.**

## Introduction

Although the formation of the cerebral cortex is extremely complex, it can be grossly broken down into three main steps: cell proliferation, cell migration and cortical organization [1]. Cells proliferate in the germinal zones, within and adjacent to the walls of the lateral ventricles, then migrate along various pathways to the developing cortex where they disengage from the guide cell. Either during migration or after migrating into the proper cortical layer, the cells extend neurites and establish synaptic connections [2]. Disruption of these steps produces characteristic morphologic disturbances, typically abnormal sulcation and gyral patterns, that allow them to be classified into distinct entities which we have designated malformations of cortical development (MCD) (Table 1) [1].

To best classify MCD, imaging studies should be optimized. As a rule, thin-section T1- and T2-weighted mag-

netic resonance imaging (MRI) images should be acquired. For T1-weighted images, a volumetric spoiled gradient echo sequence (such as SPGR or MP-RAGE) should be acquired with partition size of 1–1.5 mm to allow the data to be reformatted in any plane. At a minimum, sagittal, coronal and axial images are necessary. For T2-weighted images, contrast between gray and white matter is best using conventional spin echo images. However, in the interest of saving time, fast spin echo (FSE; also called turbo spin echo) images might be better, especially if acquired as a 3D data set that can be reformatted. As white matter connectivity is important in function of the patient, it will become progressively more important to obtain sophisticated diffusion imaging techniques (diffusion tensor imaging, high-angular-resolution diffusion imaging, q-ball imaging) [3,4] that allow mapping of the major white matter tracts. In neonates and infants less than 10 months old (before myelination), thin-section (1.5–3 mm) heavily T2-weighted spin echo images are optimal, whereas between the ages of 10 and 24 months, thin partitions of T1-weighted volumetric spoiled gradient echo images with heavy T1 weighting are best. Beyond age 2 years, standard adult protocols should be used.

The analysis of MCD has been very useful clinically and in helping genetic counseling. In addition, however, the analysis of these disorders has greatly aided our understanding of the processes of brain development. Analysis of groups of similarly affected patients has allowed us to specify causative genes (Table 1). Identification of the protein products of those genes often reveals involvement of those proteins in previously unsuspected pathways, and identification of those pathways leads to discovery of other causative genes. An excellent example of this process has been the analysis of congenital muscular dystrophies with CNS involvement. Once it was found that the biochemical problem in these disorders is impaired O-glycosylation of  $\alpha$ -dystroglycan, mutations of many of the genes involved in that process were rapidly identified [5].

In the following sections, the genetic, imaging and functional aspects of some of the most common MCD will be discussed along with the options for treatment of associated epilepsy.

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**Table 1. Genetic malformations of cortical development**

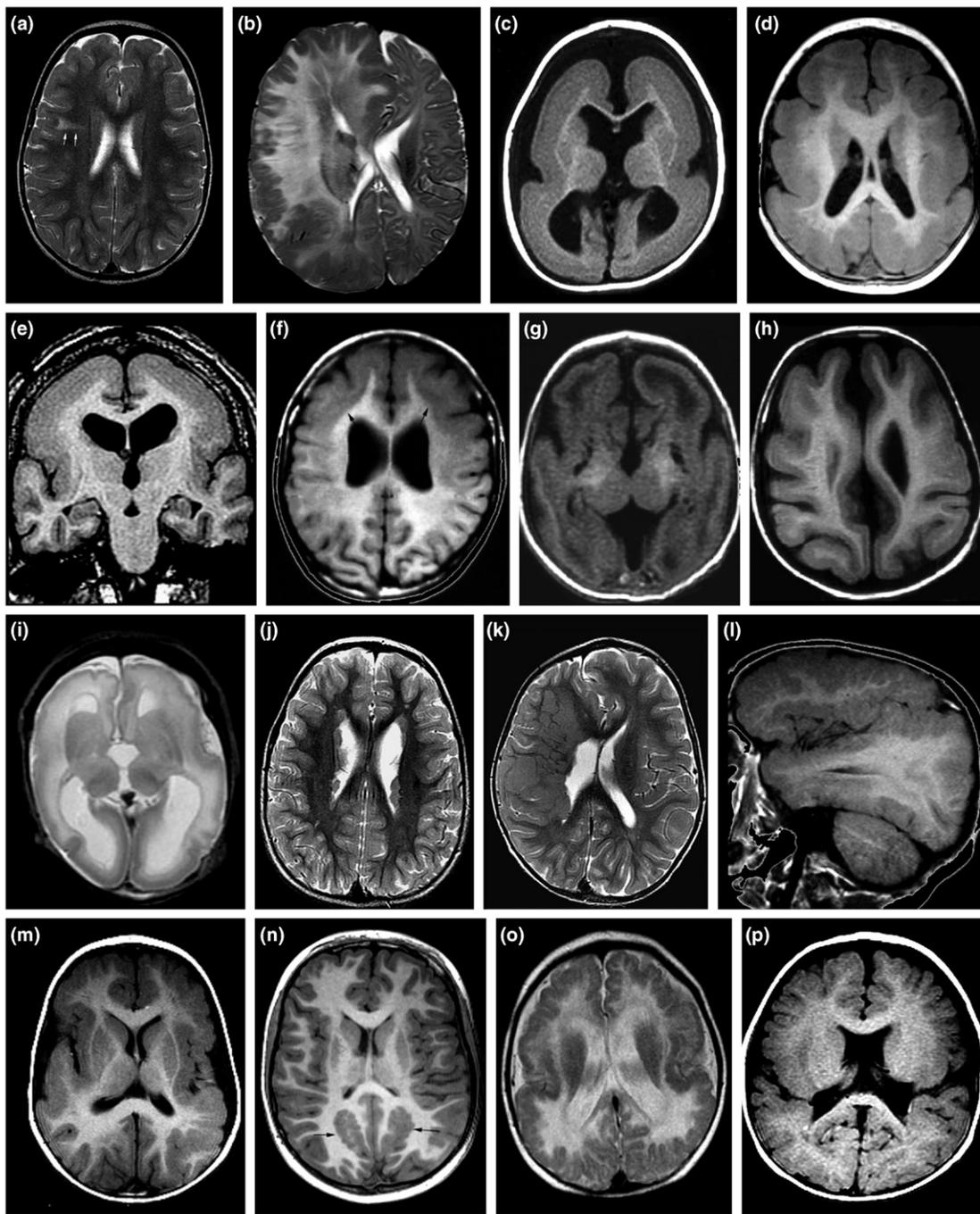
Malformation	Gene	Locus	Refs
<b>Malformations from abnormal proliferation</b>			
Focal cortical dysplasia			
Tuberous sclerosis	<i>TSC1</i>	9q34.13	[75]
Tuberous sclerosis	<i>TSC2</i>	16p13.3	[75]
<b>Malformations from abnormal migration</b>			
Lissencephaly (XL, AD)			
X-linked lissencephaly with abnormal genitalia	<i>ARX</i>	Xp22.1	[15]
Isolated lissencephaly sequence (ILS) or subcortical band heterotopia (SBH)	<i>DCX</i>	Xq22.3-q23	[16]
ILS or SBH	<i>TUBA1A</i>	12q13.12	[76]
ILS or SBH	<i>LIS1</i>	17p13.3	[77]
Miller-Dieker syndrome	<i>LIS1 + YWHAE</i>	17p13.3	[78]
Lissencephaly (AR)			
Lissencephaly with cerebellar hypoplasia (LCH) group b	<i>RELN</i>	7q22.1	[79]
LCH group b	<i>VLDLR</i>	9p24.2	[21]
Heterotopia (XL, AD)			
Periventricular nodular heterotopia (PNH)	<i>FLNA</i>	Xq28	[23]
PNH	–	5p15.1	[25]
PNH	–	5p15.33	[25]
PNH	–	7q11.23	[26]
Heterotopia (AR)			
Microcephaly and PNH	<i>ARFGEF2</i>	20p13	[24]
Cobblestone cortical malformations (AR)			
Fukuyama congenital muscular dystrophy or Walker-Warburg syndrome (WWS)	<i>FCMD</i>	9q31.2	[80]
Muscle-eye-brain disease (MEB) or WWS	<i>FKRP</i>	19q13.32	[81]
MEB	<i>LARGE</i>	22q12.3	[82]
MEB	<i>POMGnT1</i>	1p34.1	[83]
MEB or WWS	<i>POMT1</i>	9q34.13	[84]
MEB or WWS	<i>POMT2</i>	14q24.3	[85]
Bilateral fronto-parietal cobblestone malformation (previously polymicrogyria)	<i>GPR56</i>	16q13	[86]
CEDNIK syndrome	<i>SNAP29</i>	22q11.2	[87]
<b>Malformations from abnormal cortical organization</b>			
Polymicrogyria (XL, AD)			
Rolandic seizures, oromotor dyspraxia	<i>SRPX2</i>	Xq22	[28]
Agenesis of the corpus callosum (ACC), microcephaly and polymicrogyria (PMG)	<i>TBR2</i>	3p21	[30]
Aniridia plus	<i>PAX6</i>	11p13	[29]
PMG	–	1p36.3-pter	[88]
Microcephaly, PMG	–	1q44-qter	[89]
ACC, PNH and PMG	–	6q26-qter	[90]
PMG	–	21q2	[91]
DiGeorge syndrome	–	22q11.2	[92]
Polymicrogyria (AR)			
Goldberg-Shprintzen syndrome	<i>KIAA1279</i>	10q21.3	[31]
Micro syndrome	<i>RAB3GAP1</i>	2q21.3	[32]
Schizencephaly	None known (not <i>EMX2</i> )		[93]

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

### Focal cortical dysplasia

The term focal cortical dysplasia (FCD) designates a spectrum of abnormalities of the laminar structure of the cortex, variably associated with cytopathological features including giant (or cytomegalic) neurons, dysmorphic neurons and balloon cells [6,7]. Balloon cells are of uncertain lineage, exhibit an abundant pale-staining cytoplasm, peripherally positioned nuclei, no cellular processes and cell-surface markers for pluripotent stem cells [8]. Although attempts have been made to classify FCD based on subtle histologic characteristics [6,7], no consistent nomenclature has been reached. In fact, FCD might not represent a single entity [9]. According to the prevailing hypothesis, FCD originates from abnormal migration, maturation and cell death during ontogenesis [8,10]. A developmental lineage model has been proposed in which balloon cells and dysplastic neurons are derived from radial progenitor cells in the telencephalic ventricular zone

[11]. The close cytoarchitectural similarities between FCD and the cortical tubers of tuberous sclerosis prompted the hypothesis of a common pathogenetic basis [12]. In one study, mutation analysis in patients with FCD showed a higher frequency of mild and not clearly pathogenic sequence changes in the *TSC1* (but not *TSC2*) gene in FCD compared to controls, as well as loss of heterozygosity of markers surrounding the *TSC1* gene in dysplastic compared to control tissue [12]. These results support some role for *TSC1* in the pathogenesis of FCD, although this might be small and has yet to be confirmed. Histopathologic similarities between FCD, hemimegalencephaly and the dysembryoplastic neuroepithelial tumors [9], two highly epileptogenic developmental lesions, further support the hypothesis of a developmental origin. A link has also been postulated between FCD and perinatal or early postnatal brain injury, with subsequent cell dedifferentiation in the scarred area [9,13].



**Figure 1.** Montage of cortical malformations. (a) Focal cortical dysplasia type 2b (with balloon cells) shows abnormal hyperintensity (arrows) from bottom of sulcus to ventricular wall. (b) Hemimegalencephaly has an enlarged hemisphere with abnormal sulcation and increased volume of dysplastic white matter in affected hemisphere. (c) Agyria (*LIS1* mutation) has thick cortex with almost complete lack of sulcation. (d) Pachygyria with *LIS1* mutation has more severe cortical malformation in parietal lobes than in frontal lobes. (e) Lissencephaly with *DCX* mutation has most severe cortical malformation in midfrontal lobes. (f) Band heterotopia with *DCX* (most common mutation) has an undulating band of gray matter (arrows) in frontal lobes beneath a nearly normal cortex. (g) Lissencephaly with *ARX* mutations is characterized by absent corpus callosum, dysplastic basal ganglia with cysts, and temporo-occipital agyria. (h) Lissencephaly with *RELN* mutations is characterized by less severe cortical thickening and profound cerebellar hypoplasia (not shown). (i) Two-layered lissencephaly is characterized by thin cortex, absence of corpus callosum, and moderate cerebellar hypoplasia. (j) Periventricular nodular heterotopia are nodules of gray matter intensity adjacent to the lateral ventricles. (k) Subcortical heterotopia are swirls of gray matter extending from cortex to ventricle associated with shallow sulci and diminished size of the affected region of the cerebral hemisphere. (l) Perisylvian polymicrogyria is associated with thickening of the opercular cortex and continuity of the sylvian fissure with the parietal subarachnoid space. (m) Bilateral perisylvian polymicrogyria is characterized by thickened, irregular cortex in the insulae and surrounding opercula. (n) Parasagittal parieto-occipital polymicrogyria is characterized by parasagittal infoldings of polymicrogyria (arrows) into the parietal white matter. (o) Diffuse polymicrogyria. (p) Schizencephaly describes gray matter-lined clefts extending from the subarachnoid space to the cerebral ventricle; they can be unilateral or bilateral.

The imaging findings are quite variable: the mildest malformations can be cryptic to imaging, whereas other lesions can be detected by the blurring of the cortex-white matter junction on T1-weighted images, cortical thickening or abnormal T2 or FLAIR hyperintensity in the white

matter of a gyrus or at the depth of a sulcus (Figure 1a) [14]. A band of abnormal signal intensity can be seen to extend from the cortex to the superolateral margin of the lateral ventricle; the lesion is then called transmantle dysplasia.

## Lissencephaly

Lissencephaly (including both agyria and pachygyria) is the most severe of the known malformations from abnormal neuronal migration. Less severe defects in the same genes and developmental processes result in subcortical band heterotopia. In this group of malformations, neurons begin migration but are unable to complete it. To date, mutations of six genes have been associated with lissencephaly including *LIS1*, *DCX*, *TUBA1A*, *RELN*, *VLDLR* and *ARX*, whereas co-deletion of *YWHAE* with *LIS1* appears to act as a modifier locus.

The associated phenotypes include isolated lissencephaly sequence (*DCX* in males, *LIS1* and rarely *TUBA1A*), subcortical band heterotopia (*DCX* in females and rare males, and *LIS1*), Miller-Dieker syndrome (co-deletion of *LIS1* and *YWHAE*), mild lissencephaly with cerebellar hypoplasia 'group b' or the 'disequilibrium syndrome' (*RELN* and *VLDLR*) and X-linked lissencephaly with abnormal genitalia (*ARX*). Careful review of brain imaging and other clinical features can distinguish these syndromes and usually the causative gene (Table 1).

Mutations of *LIS1* (including deletions), *DCX* and *TUBA1A* account for 65%, 12% and an unknown but small percent of patients with lissencephaly. The proteins coded by these genes all regulate microtubule and cytoplasmic dynein function and – at least for *LIS1* – interfere with neuronal migration by blocking microtubule-directed nuclear movement in ventricular zone neuroblasts, conversion of nascent postmitotic neurons to multipolar pre-migratory cells and conversion of multipolar to bipolar migratory cells. Mutations of these three genes lead to the classic form of lissencephaly in which cortical thickness is increased fourfold (3.5–4 mm to 12–20 mm) and produce a recognizable gradient in which the malformation is more severe anteriorly (*DCX*) or posteriorly (*LIS1* and *TUBA1A*).

The imaging findings of lissencephaly vary with the severity of the mutation [15–17]. When very severe, the cortex is markedly thickened and almost no sulci are formed (Figure 1c–e); when less severe, the cortex is less thickened and a variable number of shallow sulci separate broad gyri (Figure 1d,f). In some cases, a 'cell-sparse zone' is identified between the thin outer cortical layer and the thicker inner cortical layer of neurons whose migration has been arrested (Figure 1c) [18].

Mutations of *ARX* are a rare cause of lissencephaly [15], although less severe mutations result in a more common developmental disorder, cryptogenic infantile spasms [19]. This gene is a transcription factor expressed in forebrain that regulates nonradial migration of interneurons from ventral regions (ganglionic eminence) to the developing cortex [20], and has other unknown functions in the dorsal cortex. Severe seizures are presumably related to a severe deficiency of inhibitory interneurons [20], and suggest a novel developmental mechanism for some forms of early-onset severe epilepsy. Patients with *ARX* mutations have abnormalities of the basal ganglia and absence of the corpus callosum (Figure 1g) [15,19], whereas those with *RELN* and *VLDLR* mutations have less cortical thickening, absence of a cell-sparse zone and profound cerebellar hypoplasia (Figure 1h) [21,22]. The cerebral cortex of the

newly described two-layered lissencephaly [18] has only a slightly thickened cortex with few sulci, thinning of the cerebral white matter and, often, absence of the corpus callosum (Figure 1i).

## Heterotopia

Heterotopia are clusters of normal neurons in abnormal locations. The most common type, periventricular nodular heterotopia (PNH), are rests of neurons that never begin migration, remaining adjacent to the lateral ventricles (Figure 1j). To date, ~15 distinct PNH syndromes have been described [23]. The most common of these is classic bilateral PNH, which is much more frequent in females; more than 50% have mutations of the X-linked *FLNA* gene. Autosomal recessive microcephaly with PNH is a very rare phenotype caused by mutations of *ARFGF2* [24]. PNH has also been associated with copy number variations including duplication 5p15.1 or 5p15.33 [25] and deletion 6q26-q27 or 7q11.33 [26]. No genetic insights into other forms of heterotopia have been gleaned.

Heterotopia are divided into three main groups, PNH, subcortical heterotopia and leptomenigeal heterotopia, of which only the first two can be detected by imaging (so-called subcortical band heterotopia or 'double cortex' is a mild form of lissencephaly and classified in that group) (Figure 1f). PNH might be isolated – usually presenting with seizures – or part of a multiple congenital anomaly syndrome. When isolated they are often X linked, and affected patients develop normally until the onset of epilepsy, which appears in ~72% and at variable ages [23]. Subcortical heterotopia are sporadic, irregular, curvilinear accumulations of gray matter nodules that course from the ventricular surface to the cortex, which is often thin and microgyric. The ipsilateral hemisphere is typically small and the basal ganglia is small and irregular (Figure 1k). Affected patients have epilepsy and might have accompanying neurologic signs/symptoms.

## Polymicrogyria

The term polymicrogyria defines an excessive number of abnormally small gyri that produce an irregular cortical surface. It is a very common cortical malformation and is associated with a dizzying array of patterns and syndromes. Its pathogenesis is not understood; brain pathology demonstrates abnormal development or loss of neurons in middle and deep cortical layers [27], variably associated with an unlayered cortical structure. Today, polymicrogyria has been associated with mutations of only a few genes including *SRPX2* [28], *PAX6* [29], *TBR2* [30], *KIAA1279* [31], *RAB3GAP1* [32] and *COL18A1* [33], with all but *SRPX2* found in rare syndromes.

Developmental studies are available for only *PAX6* and *TBR2*, but these suggest one potentially interesting mechanism. Specifically, the mouse homologs of these two genes plus the mouse *Tbr1* gene are expressed sequentially by radial glia (*Pax6*), intermediate progenitor cells (*Tbr2*) and postmitotic neurons (*Tbr1*) in developing neocortex, a developmental pathway that produces many cortical projection neurons, so far best shown for deep cortical layers. Disruption of this pathway can lead to loss or altered fate of large cortical neurons. The *SRPX2* gene maps to band

Xq23, and does not account for X-linked forms of perisylvian polymicrogyria that map to Xq27 and Xq28.

A disorder referred to as bilateral frontoparietal polymicrogyria (BFPP) is associated with mutations of a gene named *GPR56*. *GPR56* codes for a G-protein-coupled receptor that is expressed in neuronal progenitor cells of the ventricular and subventricular germinal zones during periods of neurogenesis [34]. Normally, the GPR56 protein undergoes two major modifications, GPS domain-mediated protein cleavage and N-glycosylation; the N-terminal fragment can be released from the cell surface [35]. It appears that mutations in *GPR56* result in impaired trafficking of the mutant protein to the plasma membrane [35]. The imaging characteristics of BFPP (myelination defects, cerebellar cortical dysplasia with cysts, frequent involvement of the medial aspects of the cerebral hemispheres) resemble more those of the so-called cobblestone malformations (muscle-eye-brain disease and Fukuyama congenital muscular dystrophy) that are also associated with N-glycosylation defects in the developing brain. Therefore, this disorder might be best classified as a cobblestone malformation.

The imaging appearance of polymicrogyria varies with the age of the patient [36]. In newborns and young infants, the polymicrogyric cortex is very thin, with multiple, very small undulations. After myelination, polymicrogyria appears as slightly thick cortex with a slightly irregular cortex-white matter junction. The pial surface might appear paradoxically smooth, as a result of fusion of the molecular layer (cortical layer 1) across adjacent microgyri. Polymicrogyria can be localized to a single gyrus, involve portions of a hemisphere (Figure 1l), be bilateral and asymmetrical, bilateral and symmetrical (Figure 1m,n) or diffuse (Figure 1o). Sometimes, it is associated with deep clefts that might extend through the entire cerebral mantle to communicate with the lateral ventricle (schizencephaly) (Figure 1p).

Extent and location of the cortical abnormality influence the severity of neurologic manifestations. Polymicrogyric cortex in language-related areas, around the left perisylvian fissure, was identified at autopsy in individuals with developmental dysphasia or dyslexia [37,38] and is considered to be an important cause of the developmental language disorder [39]. Mutations of the *SRPX2* gene have been associated with bilateral perisylvian polymicrogyria, which is regularly accompanied by oral and speech dyspraxia, but also with oral and speech dyspraxia and seizures in individuals with normal brain MRI [28]. These observations, and the finding that the orthologous gene *SrpX2* is not detected during murine embryogenesis, suggest a major role for *SRPX2* in the development and functioning of language-related areas in humans.

### **Epileptogenesis, aberrant circuits and reorganization of cortical function: implications for surgical treatment of epilepsy in malformations of cortical development**

Although not all MCD are equally epileptogenic, epilepsy is the most common clinical manifestation. Treatment with antiepileptic drugs is often ineffective and no controlled trial has been performed showing that any drug treatment

is better than others in this group of malformations. When refractory to drugs, epilepsy is potentially amenable to curative treatment using a surgical approach. Diffuse MCD, involving most of the brain, such as lissencephaly, usually give rise to generalized or multifocal epilepsies and cannot be operated on. However, discrete MCD can be approached surgically in a considerable number of patients. The indications and extent of a resection will depend on the definition of the epileptogenic zone (the network of abnormally behaving neurons), which includes the ictal onset zone (i.e. the neurophysiologically defined cortical area where seizures are initiated), but does not necessarily correspond to the epileptogenic lesion. Removal of an epileptogenic lesion, without defining and removing the epileptogenic zone (lesionectomy), produces seizure control in a substantial proportion of patients, but delineation and removal of the entire epileptogenic zone, or at least the ictal onset zone, improves the outcome of lesionectomy [40]. In this section, we will review how current knowledge on epileptogenesis, abnormal circuitry and reorganization of cortical function can be translated into planning surgical treatment of epilepsy in some of the main MCD.

### *Focal cortical dysplasia*

Virtually in all patients with FCD the lesion is detected after onset of focal epilepsy, but very early seizure onset has been associated with infantile spasms with focal features [41]. FCD is a frequent cause of focal status epilepticus [41] and the most common pathological substrate in epilepsy surgery series, reaching up to 40% [9]. Recordings with intracranial electrodes have demonstrated that the epileptogenic zone often extends beyond the lesion identifiable by MRI [7,10] and revealed complex propagation patterns with unexpected interactions between noncontiguous sites [42]. Surface and intracranial EEG recordings reveal focal positive spike discharges or fast EEG frequencies, and ablation of tissue exhibiting these electrographic patterns correlates with outcome [43,44]. Although some patients can be operated on without invasive intracranial recordings, the best results are obtained when surgery is guided by stereo-EEG investigations [7] rather than by subdural grids [44].

Numerous studies on surgically resected human dysplastic tissue have focused on the mechanisms of epileptogenicity. Correlative light and electron microscopic methods indicate that balloon cells do not receive synaptic contacts, whereas abnormally large ectopic neurons are surrounded by hypertrophic basket formations [45]. The density of excitatory and inhibitory synapses differs from that in the adjacent normal cortex, exhibiting increases and decreases in synaptic density as well as changes in the proportion of excitatory and inhibitory synapses; these might result in multiple changes in excitatory and inhibitory circuits [45].

Extensive modifications in neurotransmitter receptors have been reported. The NMDA NR2A/B, NR2B and NR1-1a, 1b, 2a, 2b and GluR2/3 receptors are increased in dysplastic neurons [10]. Increased or decreased expressions of glutamate and GABA subunit mRNA receptors have also been observed [46].

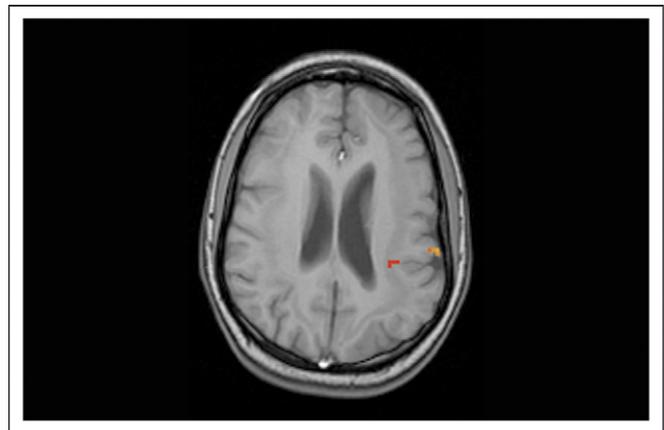
Disrupted ionic homeostasis might contribute in rendering dysplastic tissue highly epileptogenic. Individual cytomegalic neurons exhibit abnormal intrinsic membrane properties as they are more excitable, exhibit increased capacitance, decreased resistance and longer time constants [47]. Electrophysiological studies have indeed revealed that GABA<sub>A</sub> receptor activation induces large increases in extracellular K<sup>+</sup> concentration, leading to synchronous potentials and sustained ictal-like activity [48]. KCC2, a neuron-specific K<sup>+</sup>-Cl<sup>-</sup> co-transporter serving as a Cl<sup>-</sup> extrusion mechanism, has an altered subcellular distribution in dysplastic neurons [49]. Failure in reducing intracellular Cl<sup>-</sup> concentration enough to render GABA<sub>A</sub> response inhibitory might play a role in epileptogenesis [49].

Electrical stimulation studies have shown that the dysplastic neocortex might conserve temporal and frontal language sites [50], but atypical motor homunculi have been revealed [42]. Magnetic source imaging suggests that, when FCD involves the sensorimotor cortex, reorganization of sensory function is observed outside the malformed area [51]. Correlative cortical stimulation and histopathologic studies suggest absence of language or motor functions in epileptogenic perirolandic and Broca's areas that exhibit histopathological evidence of FCD with balloon cells and preservation of motor functions when no balloon cells are present [52]. Although one might argue that the higher the disruption of cortical lamination the lower the ability of the cortex to subserve function, individual variability probably exists and extrapolation of results to the whole population of patients with FCD is probably not possible [45].

### Heterotopia

Depth electrode recordings have demonstrated that seizure initiation might occur within the heterotopic nodule(s) [53], at a distance in the neocortex or simultaneously in both [54]. When nodular heterotopia is located in the temporal lobe, seizure initiation can involve the hippocampus [55]. Functional MRI studies have confirmed that PH can be functionally integrated in complex circuits and participate, for example, in motor activity [56]. The practical implications are obvious: when considering surgical treatment of epilepsy in nodular heterotopia, invasive exploration with depth electrodes is required to improve localization and is the key to a better outcome [53–55]. Demonstration of a focal, rather than extended, epileptic generator is the best predictor of a good surgical outcome [55]. Surgical procedures performed before these concepts became clear resulted in poor outcomes [57]. Blood oxygenation level-dependent (BOLD) changes during continuous EEG and fMRI recording is helpful to characterize non-invasive epileptogenesis in the heterotopia and surrounding cortex and has the advantage of exploring the whole brain at the same moment [58]. This method can also be used to better define the targets for intracranial recordings but is not yet a trustworthy alternative.

Also in subcortical band heterotopia, or double cortex, fMRI and depth electrode recordings have shown simultaneous activation of functional neuronal circuitry between the heterotopic and overlying, seemingly normal



**Figure 2.** Subcortical band heterotopia as a result of *DCX* gene mutation in a young lady. Task-dependent increase of blood oxygen level-dependent signal in the primary motor cortex as well as in the underlying heterotopic gray matter in the left hemisphere.

cortex [59,60] (Figure 2). Histopathology demonstrates that heterotopic neurons settle close to the 'true' cortex in a pattern suggestive of laminar organization [61]. The normally migrated cortex and the heterotopic network are separated by a thin layer of white matter, containing all subtypes of inhibitory GABAergic interneurons, intermingled with pyramidal neurons [60]. This aberrant circuitry results in complex, and possibly multiple, epileptogenic zones [60]. Consequently, for the rare patients with this malformation who are good candidates for surgical treatment of epilepsy, depth electrodes are required [62].

Functional impairment of the cortex overlying the heterotopia is variable. [<sup>18</sup>F]deoxyglucose (FDG)-PET studies showed that nodular and laminar heterotopia have the same metabolic activity as normal cortex [63] and subsequent H<sub>2</sub><sup>15</sup>O PET studies demonstrated that the overlying cerebral cortex can either retain its expected map of functional activation or show extensive reorganization, even when appearing structurally normal on MRI [64]. Extensive reorganization of the topographic pattern of activation is also suggested by cortical stimulation studies [65].

### Polymicrogyria

Numerous observations have linked polymicrogyria with a spectrum of epilepsy phenotypes and patterns of reorganization of cortical function. Epilepsy related to polymicrogyria has variable severity, including cases with good outcome and spontaneous remissions, even after a period of intractability [66]. However, diffuse epileptogenesis is frequently encountered, even with seemingly limited abnormalities [67]. Intracranial recordings suggest large epileptogenic networks which extend well beyond the limits of the visible abnormality [67,68]. Consequently, surgical treatment of epilepsy is applicable to a very limited number of patients in whom large resections are feasible [68] and remission of epilepsy is not expected [66].

Epileptogenicity of polymicrogyria and its mechanisms are not known, but a considerable number of patients do not have epilepsy [41]. Experimental models produced by localized freezing suggest widespread

functional disruption, with downregulation of different GABA<sub>A</sub> receptor subunits extending far beyond the visualized abnormality [69].

Functional studies suggest variability in cortical representation, probably in relation to both the severity of anatomic disruption and the involved modality. Magnetic source imaging studies show that the somatosensory function remains localized in the polymicrogyric rolandic cortex, as long as anatomy is not distorted by a schizencephalic cleft, in which case function is located in the hemisphere ipsilateral to stimulation, in expected anatomic locations [51]. fMRI studies indicate that the polymicrogyric language and motor areas tend to preserve functionality in the expected sites [70]. Combined transcranial magnetic stimulation and fMRI studies in patients with hemiparesis and polymicrogyria suggest that ipsilateral corticospinal projections from the contralesional hemisphere to the paretic hand, corticospinal projections to the paretic hand originating in the polymicrogyric cortex and bilateral motor representation are all possible [71,72]. Therefore, participation in motor functions varies from corticospinal ('primary') motor control, to putative participation as 'nonprimary' motor areas, to absence of any functional participation [71]. Conversely, the somatosensory function would be more prone to reorganization within the malformed hemisphere, with interhemispheric sensory-motor dissociation being possible [72]. Normal organization of visual areas and processing of visual information has been observed in patients with bilateral parieto-occipital polymicrogyria, using cognitive testing and phase-encoded retinotopic mapping analysis [73,74]. Generalization of findings to the entire population of patients with polymicrogyria might be inappropriate, however, in view of its causal heterogeneity and high degree of histopathologic variability [67].

## Conclusion

MCD are an important cause of drug-resistant epilepsy. Some patients have obvious neurological impairment, but others show unexpected deficits that are detectable only by screening. Although no translational insights at the molecular pharmacological level have clearly emerged that might specifically target MCD-related epileptogenesis, the role of surgical treatment of epilepsy and its strategies are now relatively established. Localization of function based on anatomic landmarks might not be reliable, and intracranial recordings have shown a high propensity for complex epileptogenic networks that might include remote cortical and subcortical regions. The MRI visible area of cortical abnormality should therefore be regarded as just a marker of the epileptogenic zone rather than its tangible substrate. Completeness of resection, after delineation of the ictal onset zone, a key factor for successful epilepsy surgery, might be particularly difficult. Invasive EEG monitoring is necessary in most patients [7,42]. Future advances in imaging techniques and molecular markers will possibly improve the identification of the epileptogenic zone. Neural plasticity issues are of primary importance to surgical planning, as the possibility of removing eloquent cortex permits more complete procedures with potentially higher rates of success.

However, the functional consequences of malformative lesions are still poorly understood; conservation of function in the dysplastic cortex, its atypical representation and relocation outside the malformed area are all possible. Surgical planning for associated epilepsy should therefore be based on individual assessments of structural imaging and of the major functions relevant to the area in question in any such patient.

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