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Neuronal migration disorders : Focus on the cytoskeleton and epilepsy

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Overview

A wide spectrum of focal, regional, or diffuse structural brain abnormalities, collectively known as malformations of cortical development (MCD), frequently manifest with intellectual disability (ID), epilepsy, and/or autistic spectrum disorder (ASD). As the acronym suggests, MCD are perturbations of the normal architecture of the cerebral cortex and hippocampus. The pathogenesis of these disorders remains incompletely understood; however, one area that has provided important insights has been the study of neuronal migration. The amalgamation of human genetics and experimental studies in animal models has led to the recognition that common genetic causes of neurodevelopmental disorders, including many severe epilepsy syndromes, are due to mutations in genes regulating the migration of newly born post-mitotic neurons. Neuronal migration genes often, though not exclusively, code for proteins involved in the function of the cytoskeleton. Other cellular processes, such as cell division and axon/dendrite formation, which similarly depend on cytoskeletal functions, may also be affected. We focus here on how the susceptibility of the highly organized neocortex and hippocampus may be due to their laminar organization, which involves the tight regulation, both temporally and spatially, of gene expression, specialized progenitor cells, the migration of neurons over large distances and a birthdate-specific layering of neurons. Perturbations in neuronal migration result in abnormal lamination, neuronal differentiation defects, abnormal cellular morphology and circuit

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formation. Ultimately this results in disorganized excitatory and inhibitory activity leading to the symptoms observed in individuals with these disorders.

Human neuronal migration disorders

Type I lissencephaly

The prototype of a so-called ‘neuronal migration disorder’ is lissencephaly, which literally means “smooth brain” (derived from Ancient Greek). Type I, also known as classical lissencephaly, consists of a group of related neuronal migration disorders. Included in this spectrum are agyric (without gyri), pachygyric (simplified gyri) and subcortical band heterotopic (abnormally positioned neurons, SBH) forms (Barkovich et al., 2012; Francis et al., 2006). Patients with severe type I lissencephaly exhibit ID and epilepsy, the latter often pharmaco-resistant. Post-mortem studies of lissencephalic brains have identified at least four patterns of cortical disorganization (Forman et al., 2005). The most commonly observed shows the replacement of the normal six layer neocortex with a markedly thickened four layer cortex (Forman et al., 2005). Pathologic review of these brains suggest a roughly inverted cortex with large pyramidal neurons normally found in layer 5 appearing superficially, just below the molecular layer (layer 1) to form an abnormal layer 2. Below this layer, forming a very thick (up to several centimeters) layer 4 that extends down to the white matter, is a disorganized collection of neurons, believed to normally populate layers 2–4. Intercalated between the layer of pyramidal neurons and the deep layer of smaller neurons is a relatively cell sparse layer that appears by early childhood, representing layer 3. Although the gyral pattern is severely affected, in most cases the brain appears to be normal size at birth; however, postnatal microcephaly is often associated with agyric cases (Pavone et al., 1993). Pachygyria is associated with a similarly disorganized cortex, although the presence of large simplified gyri suggests a different (potentially better) organization of neurons in some regions compared to agyria. The characteristics of different types of human MCD and associated genes are described below and summarized in Table 1.

The study of families with single and multiple affected individuals aided the discovery of a number of type I lissencephaly genes, often related to the microtubule cytoskeleton. The first to be identified was *lissencephaly 1 (LIS1)* (Reiner et al., 1993). Mutations in *LIS1* (*PAFAH1B1*, *platelet-activating factor acetylhydrolase 1b, regulatory subunit 1*), along with mutations in *doublecortin (DCX)* (des Portes et al., 1998b; Gleeson et al., 1998), explain a majority of type I lissencephaly cases. There are subtle differences in patients with mutations in these two genes. *LIS1* mutations are associated with a more severe phenotype in the posterior aspects of the cerebral hemispheres (occipital lobes more severe than frontal lobes), whereas patients with *DCX* mutations often have the reverse gradient (Pilz et al., 1998). *DCX* is located on the X-chromosome, thus almost all agyric individuals are males (female patients frequently have SBH, see below, (des Portes et al., 1998a), whereas *LIS1* is located on the short arm of chromosome 17, and thus heterozygote mutations show an equal frequency in males and females. Large deletions of chromosome 17 that include *LIS1* and adjacent genes, importantly *14-3-3ε* (*YWHAE*, *tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon*), are responsible for the more severe Miller-Dieker syndrome (Reiner et al., 1993; Toyo-oka et al., 2003). This latter protein binds to

phosphoproteins, including a number involved in cell division, and plays a role in intracellular signaling. In addition to mutations in *LIS1* and *DCX*, less common but well-established causes of similar forms of lissencephaly include mutations in a number of other genes. This includes another X-linked form (X-linked lissencephaly with ambiguous genital, XLAG syndrome) associated with mutations in a transcription factor, *aristaless-related homeobox (ARX)* (Kato et al., 2004; Kitamura et al., 2002). This form of lissencephaly has an unusual three-layer cortex, commonly accompanied by agenesis of the corpus callosum, and is typically neurologically devastating.

Mutations in certain cytoskeletal proteins are viable in the heterozygote state, causing a range of MCD. Gain-of-function (autosomal dominant) mutations in two actin genes, *ACTB* and *ACTG1*, have been found in patients with Baraitser–Winter syndrome, which affects development of several parts of the body including the brain (Verloes et al., 2015). Mutations in three tubulin genes, *TUBA1A*, *TUBB2B*, and *TUBG1*, have all been associated with forms of cortical gyral malformations (Friocourt et al., 2011; Jaglin et al., 2009; Keays et al., 2007; Poirier et al., 2007; Poirier et al., 2013). *TUBA1A* and *TUBB2B*, both strongly expressed in post-mitotic neurons, are mainly associated with agyria/pachygyria and polymicrogyria (see below), respectively, but there is also phenotypic overlap in some patients with anatomical abnormalities in several other brain structures (Cushion et al., 2013; Jaglin and Chelly, 2009). Affected patients display severe ID and early-onset epilepsy, and recently mutations have also been implicated in ASD (Neale et al., 2012; Pinto et al., 2010). *TUBB3* mutations are also associated with diverse spectrum of brain abnormalities that suggest abnormal migration and axon guidance defects (Poirier et al., 2010). *TUBB5* mutations in humans result in microcephaly as well as other structural abnormalities and cognitive disorders (Breuss et al., 2012). *TUBG1*, which encodes one of two human gamma-tubulins, is highly expressed in the fetal brain and functions in tubulin nucleation (Kollman et al., 2011), and mutations also lead to lissencephaly and/or microcephaly (Poirier et al., 2013).

Lissencephaly with severe cerebellar hypoplasia (abnormally small or missing cerebellum) has been identified in patients with *reelin (RELN)* mutations (Hong et al., 2000), a phenotype also observed in some patients with *TUBA1A* mutations and less commonly *TUBB2B* (Bahi-Buisson et al., 2008; Fallet-Bianco et al., 2008; Jaglin and Chelly, 2009; Keays et al., 2007). *Reelin* codes for a secreted extracellular matrix protein (see below). Patients with mutations in the Reelin receptor, *VLDLR (very low density lipoprotein receptor)*, also appear to have cortical malformations in this spectrum, often with pontocerebellar hypoplasia, cerebellar ataxia associated with ID, or disequilibrium syndrome, e.g., (Schlotawa et al., 2013). Finally, a relatively rare form of lissencephaly called microlissencephaly has been found to associate with mutations in *NDE1 (nuclear distribution gene E homolog 1)*, (Alkuraya et al., 2011). As suggested by its name, the protein almost certainly plays a role in nuclear migration, as originally identified in *Aspergillus nidulans*. A recent review nicely classifies all of these mutations (Fry et al., 2014).

SBH is categorized in the same spectrum as agyria (Pinard et al., 1994). The difference between the two appears to be natural (X inactivation) or somatic mosaicism. In SBH there is generally a normal, or relatively normal, overlying cortex and gyral pattern. However,

collections of misaligned neurons, usually organized as small nodules, coalesce just below the cortex but are separated from it by a band of white matter. The neurons in the cortex proper are assumed to have migrated normally whereas those in the subcortical location appear to have failed to fully migrate during development. Most cases of SBH occur in females harboring one mutant allele of *DCX* (des Portes et al., 1998b). It is generally assumed, and supported by mosaic analysis, that homotypic cortical neurons have inactivated the mutant allele during random X-inactivation (Lyonization), whereas those in the heterotopia have inactivated the normal allele (Gleeson et al., 2000). This same mechanism, via somatic mosaicism, has been identified for other patients with SBH and *LIS1* mutations, or males with *DCX* mutations (Sicca et al., 2003). SBH are almost always associated with epilepsy, which may or may not be pharmaco-resistant (Bahi-Buisson et al., 2013; Guerrini and Marini, 2006). Overall, *DCX* and *LIS1* genes explain a large proportion (~80 %, Bahi-Buisson et al., 2013) of SBH cases, with *DCX* explaining the vast majority of them (Bahi-Buisson et al., 2013; des Portes et al., 1998a).

Interneuronopathies

Cell migration defects that affect cortical interneurons (INs) have also been characterized. These neurons are derived from distinct progenitor zones in the ventral telencephalon (see below), namely the medial and caudal ganglionic eminences (MGE and CGE). In contrast to the radial migration of projection neurons from the dorsal cortical progenitor zone, the circuitous migration of INs from the ventral GEs is controlled by separate guidance cues (see below). Perturbations in the development and/or migration of these neurons have been implicated in a variety of disorders, particularly those with epilepsy, ID and autism (e.g., Rett syndrome). Collectively these disorders have been labeled “interneuronopathies”. While IN deficits have been documented in several human conditions including lissencephaly associated with *LIS1* (Pancoast et al., 2005) and *ARX* (Marcorelles et al., 2010) mutations, in fact relatively few human MCD have been directly linked to IN defects. In contrast, a growing body of literature has linked IN migration and function to epilepsy (e.g., (Kitamura et al., 2009; Nasrallah et al., 2012) and behavioral abnormalities, including ASD-like symptoms (Chao et al., 2010; Rubenstein and Merzenich, 2003).

Periventricular heterotopia (PVH)

PVH is another intriguing X-linked “neuronal migration” condition that is also believed to be mechanistically related to mosaicism. In this disorder the heterotopia are present as nodules of grey matter positioned very closely to, or extruding into the ventricles, and this is associated with a relatively normal-appearing cortex using magnetic resonance imaging (MRI). In this malformation a subset of neurons cannot or do not initiate migration from their site of production. This disorder is associated with mutations in X-linked *Filamin A* (*FLNA*), coding for an actin-binding protein, and is frequently lethal in males, hence predominantly identified in females, who generally suffer from severe epilepsy (Fox et al., 1998; Parrini et al., 2006). *FLNA* is also expressed in developing blood vessels and other cell types, leading to co-morbidities (Feng et al., 2006; Robertson et al., 2006). Other cases of autosomal PVH exist due to mutations in related genes, including *ARHGEF2* (*Rho/Rac guanine nucleotide exchange factor (GEF) 2*), *C6orf70* (*chromosome 6 open reading frame 70*), *FAT4* (*atypical cadherin 4*, a member of the protocadherin family) and *DCHS1*

(dachsous1, cadherin-related 1 (Cappello et al., 2013; Conti et al., 2013; Sheen, 2014; Sheen et al., 2004). Each of these five genes codes for proteins that play roles at the membrane, either in trafficking or in cell-cell or adhesive complexes (Bizzotto and Francis, 2015). Many cases of PVH remain unexplained genetically. Interestingly, progenitor abnormalities may be the primary event causing this disorder (Carabalona et al., 2012; Sheen, 2014), suggesting that neuronal migration abnormalities could be a secondary consequence of a perturbed migratory environment.

Type II lissencephaly

Type II lissencephaly (also known as cobblestone lissencephaly) is clinically, genetically, mechanistically and histologically distinct from type I lissencephaly (Fry et al., 2014). The surface of the brains from patients with type II lissencephaly typically have a loss of gyri with a “lumpy and bumpy” overall appearance, reminiscent of cobblestones, thus the alternate name. In addition to the cerebral hemispheres, the cerebellum is often similarly affected. The cortex in this condition is much thicker than the normal cortex, but typically thinner than in classical lissencephaly, averaging about 1 cm in the mature brain (Fry et al., 2014). The pathogenesis of these conditions is decidedly different from type I lissencephaly. In contrast to the migration defects found in all of the disorders described above, type II lissencephaly results from an over-migration of neurons. During development migrating neurons breach the pial-glial limitans and invade the overlying subarachnoid space. This breach gives rise to almost a ‘rind’ of neuroglial and connective tissue covering the brain, accounting for the surface appearance. The pathogenesis of this spectrum of disorders, which includes the Walker-Warberg syndrome, Fukuyama congenital muscular dystrophy, and muscle-eye-brain disease, has been partially elucidated through the identification of causative genes. At least half of patients with these disorders have mutations in *POMT1*, *POMT2*, *POMGNT1*, *FKTN*, *FKRP* or *LARGE*, all O-glycosylases (Mercuri et al., 2009). The primary target for the glycosylation is α -dystroglycan, which is highly expressed in the pial-glial limitans; loss of the O-glycosylation leads to perturbed neuroprogenitor basal attachments at the surface of the brain, causing breaks in the basement membrane and resulting in the over-migration of neurons and the resulting cobblestone phenotype (Moore et al., 2002).

Polymicrogyria (PMG)

In other areas where the pial-glial limitans is perturbed but neurons do not necessarily migrate out, the result is PMG, a cortical malformation pattern frequently found associated with type II lissencephaly. Although there is some overlap, PMG may also exist as a separate entity (Stutterd and Leventer, 2014), and is characterized by an excess of small gyri that may or may not be fused together, with abnormal development or loss of neurons from middle and deep cortical layers, resulting in variable lamination patterns and excessive folding (Guerrini and Dobyns, 2014). Clinical manifestations include a high incidence of epilepsy with variable types and age of onset (Guerrini and Dobyns, 2014; Stutterd and Leventer, 2014). Patients with bilateral bifrontoparietal PMG, which is associated with mutations in *GPR56* (*G protein-coupled receptor 56*), often have ID and epilepsy, white matter abnormalities and cerebellar dysplasia (Bahi-Buisson et al., 2010). Mutations in other genes including the transcription factors *PAX6* (Glaser et al., 1994) and *TBR2* (Baala et al., 2007),

and the tubulin gene, *TUBB2B* are all recognized in human (Bizzotto and Francis, 2015; Takano, 2011). Unlike other MCD, non-genetic causes are also recognized, including prenatal vascular problems and infections (Guerrini and Dobyns, 2014; Takano, 2011). *TUBA1A* is also now associated with PMG in several patients (Bahi-Buisson et al., 2010; Cushion et al., 2013), a gene more closely associated with agyria/pachygyria. *SRPX2* (*sushi-repeat containing protein, X-linked 2*), coding for a secreted proteoglycan, is also involved in a wide-spectrum, with PMG a rare occurrence in some patients (Roll et al., 2010; Royer-Zemmour et al., 2008). With the advent of whole exome sequencing, there indeed seem now to be overlaps, initially unexpected, between a number of cortical malformations, breaking down the barriers between them, but not always clarifying the cellular mechanisms involved.

Microcephaly

In primary microcephaly (MCPH) the brain is significantly smaller in size than age-matched control brains, and this is associated with ID. In autosomal recessive MCPH forms, the architecture of the brain seems not to be dramatically changed (Barbelanne and Tsang, 2014; Bizzotto and Francis, 2015; Francis et al., 2006). The small brain size is associated with a significantly reduced number of neurons, with converging evidence from the mouse suggesting a depleted progenitor pool, due to abnormalities often leading to cell death. Mutations in *ASPM* (*abnormal spindle-like microcephaly-associated*) represent the most common cause of MCPH. This protein functions at the spindles during cell division (Fish et al., 2006). Similarly, *MCPH1* deficiency is due to imbalanced centrosomal maturation leading to abnormal spindles, which has effects on the cell cycle (Gruber et al., 2011). Another gene *STIL* (*SCL/TAL1-interrupting locus*), encodes a centriole-duplication factor; its absence completely blocks centriole amplification (Arquint and Nigg, 2014). Mutations in *CDK5RAP2* (*cyclin-dependent kinase 5 related activator protein 2*) involved in centrosome function, have been shown to lead to mitotic delay with cells exhibiting abnormal spindle poles (Lizarraga et al., 2010). *CENPJ* (*centromeric protein J*) is also involved in centrosome and spindle integrity (Insolera et al., 2014). Also, *CEP63* and *CEP152* form a complex involved in regulating centrosome numbers and defects in either result in a diminished pool of progenitors (Sir et al., 2011). Thus, each of these proteins has effects on centrosome and spindle pole formation and function affecting progenitor cells. There are also a number of related forms that have more severe consequences on the architecture of the brain (e.g., microcephaly with a simplified gyral pattern (MSGP) and/or microlissencephaly). Genes such as *WDR62* (*WD repeat-containing protein*), *NDE1* and *KIF5C* are involved in these forms, and these also play a role in centrosome and spindle pole-related functions (Bizzotto and Francis, 2015; Yu et al., 2010). Overlap between primary microcephaly, MSGP and microlissencephaly has not surprisingly also been identified, e.g., involving genes such as *WDR62* and *ASPM*.

Neurodevelopment

Here we describe the major steps of prenatal brain development in mammals, focused on the unique aspects of cortical development. Table 2 compares major cortical events in human and rodent taking place during development, and comparative stages were also schematized

in Jaglin and Chelly (2009). We also briefly refer to gliogenesis (Bercury and Macklin, 2015; Tabata, 2015), also discussed in another article of this issue.

Early brain development and development of the cortical wall

The earliest stages of brain development involve segmentation of the neural tube into lineage-restricted compartments that are defined by the expression of a specific set of genes (Lim and Golden, 2007; Puelles and Rubenstein, 1993; Stiles and Jernigan, 2010; Sur and Rubenstein, 2005; Wilson and Rubenstein, 2000). The most anterior subdivision is called the prosencephalon, which gives rise to all forebrain structures, followed immediately posteriorly by the mesencephalon (midbrain) and rhombencephalon (hindbrain). As development proceeds, the prosencephalon is further divided into the more anterior telencephalon, which gives rise to the neocortex, hippocampus and basal ganglia; and the diencephalon, giving rise predominately to the thalamus.

Throughout the brain, the germinal layer is constituted by a proliferative, pseudo-stratified neuroepithelium containing progenitor cells that produce neurons and glia (Kriegstein and Alvarez-Buylla, 2009; Rakic, 2009). It consists of a ventricular zone (VZ), the most apical region lining the ventricle, followed by a subventricular zone (SVZ), both of which contain neuroprogenitors (Fig. 1). The most superficial/basal layer is called the marginal zone (MZ), which is occupied by a horizontally organized, transient population of Cajal-Retzius (CR) neurons (Fig. 1). Born at E10.5–12.5 in the mouse, CR cells migrate tangentially from three different sources to spread evenly around the cortex (Bielle et al., 2005) where they have an imperative role in regulating neuronal migration via secretion of reelin and other factors (see below).

In the dorsal telencephalon (also called the pallium), the first cohort of VZ-derived post-mitotic neurons migrates toward the pial surface to form the cortical preplate at E11.5, which is subsequently split into two layers around E13, the subplate and the MZ (Ayala et al., 2007; Gupta et al., 2002). The intermediate zone (IZ) forms above the SVZ, containing radially migrating neurons, the processes of radial glial (RG) cells, and axons from neurons that have arrived in the cortical plate (CP, Fig. 1). Neurogenesis peaks around E14 in the mouse, and is completed by birth in most mammals (Gupta et al., 2002; Spitzer, 2006), although discrete sites continue to generate neurons and glia in the adult brain (Kriegstein and Alvarez-Buylla, 2009).

Neuroprogenitors

RG cells, derived from neuroepithelial cells, are the predominant population of neuronal precursor cells after the onset of neurogenesis at E10 (Pinto and Gotz, 2007). Their somata are located in the VZ throughout the developing brain. They are likely to be heterogeneous in location, time of development, maturity and gene expression patterns that influence the fates and positions of their progeny (Pinto and Gotz, 2007). They are characterized by long basal, radial processes that extend from the VZ to the pial surface, as well as short apical processes that contact the ventricular lining (Rakic, 1972). CR cells are critical for maintaining RG basal attachments (Frotscher, 1998; Hartfuss et al., 2003), as are other components of the extracellular matrix (Elias and Kriegstein, 2008; Franco and Muller,

2011). These contacts remain during mitosis and interkinetic nuclear migration (Miyata et al., 2001; Wang et al., 2011a). RG cells can divide symmetrically to produce two RG daughter cells, or asymmetrically, when one daughter cell retains the RG phenotype, and the second either acquires a post-mitotic neuronal fate or becomes a restricted neuronal progenitor in the SVZ (Fig. 1b–d). Mitotic spindle orientation has frequently been discussed related to these division modes because it may potentially affect fate, or at least attachment to the ventricular lining (for discussions of this subject see (Bizzotto and Francis, 2015; Lancaster and Knoblich, 2012). Although there is evidence that some RG cells are lineage-restricted early on to either produce neurons *or* glia throughout development (Pinto and Gotz, 2007), recent studies using new methods for clonal analysis also support the classical view that RG cells first generate neurons/neurogenic progenitors and then glia (Gao et al., 2014; Siddiqi et al., 2014).

Other types of neuroprogenitor cells are the basal progenitors (BPs), which are mostly restricted to the telencephalon (Pinto and Gotz, 2007), and short neural precursors (SNPs), which may be a precursors to BPs. Like RG cells, SNPs divide at the VZ, but are distinguished by their lack of basal processes (Gal et al., 2006; Stancik et al., 2010). BPs can be classified as intermediate progenitors (IPs), which are multipolar and divide in the SVZ (Noctor et al., 2004). In primate brains, basal radial glia-like cells are also abundant (see below). In the mouse, IPs primarily undergo symmetric division to produce two post-mitotic neurons, and are the major source of cortical neurons (Fig. 1b; (Haubensak et al., 2004; Miyata et al., 2004; Noctor et al., 2004; Noctor et al., 2008).

In the mouse ventral telencephalon (subpallium), the SVZ is much larger compared to the pallium (Pinto and Gotz, 2007). Here a variety of progenitor types exist, and it has been suggested this region may have a primitive resemblance to the outer SVZ (see below) in primate cortices (Pilz et al., 2013). The MGE and caudal CGE are the major sites of production of neocortical INs (Butt et al., 2005; Wichterle et al., 1999). Distinct IN types are preferentially derived from each site, for example parvalbumin and somatostatin derived cortical INs are primarily derived from the MGE whereas the calretinin expressing class of INs is primarily derived from the CGE (Wonders and Anderson, 2006).

Progenitor expansion

The pallial SVZ increases in size in the later stages of neurogenesis, especially in primates, contributing to the enlargement of upper cortical layers in these species (Dehay et al., 2015). The primate SVZ can be further subdivided into two layers. The outer SVZ, not present in rodent brains, containing the outer or basal radial glial-like cell (oRGs or bRGs) (Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011), as well as a variety of minor, often transitory, progenitor forms (Betizeau et al., 2013; Dehay et al., 2015; Pilz et al., 2013). Furthermore, IPs in primate cortices can divide to produce two proliferative daughter cells (Kriegstein et al., 2006), further increasing cell number.

Patients with MCD often show the most extreme deformities in the neocortex (potentially overshadowing defects in other structures). The evolutionary changes that occurred to expand the CP, which necessitated folding to better accommodate the increased number of neurons and forming functional areas, may further render this structure susceptible to

pathology. Indeed, the neocortex represents 82 % of the human brain area, versus 42 % in the mouse (Herculano-Houzel, 2009), with about a one thousand-fold difference in surface area (Rakic, 2009). Many mutations causing MCD in humans have minimal effects in the non-gyrated rodent cortex, possibly reflecting their unique human-related roles in progenitors, gyration, or simply the increased distance travelled by neurons in the larger human brain with a thicker cortical wall.

Migration modes

Neuronal migration is classified according to the type of movement and the direction of travel relative to the radial processes of RG cells. During radial migration, cells move in general from the VZ toward the MZ through the IZ (Fig. 1). Radial migration occurs during the development of laminated structures such as the cerebral and cerebellar cortices, but also in non-laminated structures such as the spinal cord, striatum and thalamus (Ayala et al., 2007). The radial processes of RG cells serve a critical role in guiding neurons via direct contact (Rakic, 1972), with important signaling between them that is required for normal migration and maintenance of the RG process, via molecules such as ErbB (receptor), neuregulin (ErbB ligand) and connexins (gap junction proteins) (Anton et al., 1997; Elias and Kriegstein, 2008; Rio et al., 1997). During tangential migration, subpallial derived cortical INs migrate orthogonally to the radial processes (Fig. 1), navigating a complex environment with multiple signals and decision points before eventually moving radially to distribute themselves within layers (Bartolini et al., 2013). By contrast, pyramidal neurons primarily use radial migration with little tangential movement.

-Radial migration—Radially migrating neurons do not proceed directly to the pial surface, but rather undergo four stages that involve changes in polarity, migration pauses and changes of direction (Noctor et al., 2004).

These phases involve drastic changes in morphology, mediated by the underlying cytoskeleton, and a failure at any stage may contribute to the final observation of impaired migration. Prior to leaving the proliferative zones, pallial progenitors display a multipolar mode (LoTurco and Bai, 2006; Tabata and Nakajima, 2003). During this stage the cell moves little, grows small primary processes, and may be awaiting signals from the environment to induce the bipolar formation that always precedes the start of radial migration. Failure to adopt a polarized structure can cause migration delays (La Fata et al., 2014; LoTurco and Bai, 2006; Sapir et al., 2008). Genes implicated in pathways resulting in MCD, including those of the *RELN* pathway, have shown defects in multipolar migration or the transition from multipolar to bipolar migration (LoTurco and Bai, 2006; Ohshima et al., 2007). Cells may also initially descend to the VZ, before changing direction and migrating toward of the cortex (Noctor et al., 2004).

During radial migration, the same neuron may adopt different modes of movement (Nadarajah et al., 2001). Neurons migrating by somal translocation have a leading process attached at the pial surface, which upon shortening and coordination of centrosome/microtubule (MT) coupling, pulls the nucleus forward in a continuous fashion (Ayala et al., 2007; Nadarajah et al., 2001; Pinto and Gotz, 2007). Somal translocation is used at the

beginning of corticogenesis when the CP is thin, and also at end-stages of migration once cells have reached the CP (Fig. 1b–d, Franco et al., 2011). This process is independent of RG cells, unlike locomotion, which is a saltatory process that uses the RG cell fiber as a scaffold (Ayala et al., 2007; Evsyukova et al., 2013; Nadarajah et al., 2001). The latter mode is particularly required to guide the majority of neurons to the CP, and in larger, more structurally complex regions such as the gyrated cerebral cortex, oRG processes may also serve as a substrate (Hansen et al., 2010; Fietz et al., 2010; Reillo et al., 2010; Wang et al., 2011). Somal translocation and locomotion probably utilize different molecular mechanisms, e.g. reelin/Dab1 being particularly important for somal translocation (Franco et al., 2011).

Although detachment and/or non-radial alignment of RG cell fibers has been seen in mouse models of MCD, potentially causing or exasperating migration defects, curving of RG fibers occurs naturally during the development of certain regions of the cortex such as the hippocampus (Xu et al., 2014). Here migration is substantially slower than in the neocortex (Altman and Bayer, 1990; Nakahira and Yuasa 2005; Khalaf-Nazzal and Francis, 2013). Furthermore, during later stages of hippocampal formation, neurons display a “climbing mode” of migration, in which the highly branched neuronal processes of the migrating neuron may allow it to migrate in a zig-zag fashion between multiple RG fibers (Kitazawa et al., 2014). These features have not been demonstrated physiologically in other mouse brain regions so far, and may contribute to greater tangential dispersion, less specific inside-out lamination of the hippocampus compared to the neocortex, and may possibly contribute, in mouse models, to the susceptibility of the hippocampus to MCD gene mutations (Belvindrah et al 2014; Xu et al, 2014).

-Non-radial migration—Cortical IN migration, referred to as tangential or non-radial, involves a circuitous route with multiple decision points along the path. These neurons must migrate from the GE to the cortex but avoid movement into the developing basal ganglia structures (Fig. 1a). This is accomplished in part through the repulsive signaling of semaphorin 3a (Sema3a, expressed in the basal ganglia) and the receptor neuropilin-2 (Marin et al., 2001; Nobrega-Pereira et al., 2008). Ephrin-As and their receptor EphA4 play similar roles guiding INs along a corridor, avoiding the VZ or developing basal ganglia (Rudolph et al., 2010; Zimmer et al., 2008). These neurons are believed to migrate along TAG-1 positive axons, a guidance cue from the contactin family of adhesion molecules (Denaxa et al., 2005; McManus et al., 2004a), and their migration is enhanced by mitogens such as HDF1/SF (Powell et al., 2001). These processes have been reviewed recently (Bartolini et al., 2013; Guo and Anton, 2014).

Cytokine signaling has also been found to play an important role in the guidance of INs from the GE to the cortex. CXCR4, and the related modulatory receptor CXCR7, are both expressed on migrating INs. Their ligand, CXCL12 (SDF), is expressed along the migratory path. Perturbations in signaling result in a mislocalization of INs in the cortex (Lopez-Bendito et al., 2008; Sanchez-Alcaniz et al., 2011; Stumm et al., 2003; Tiveron et al., 2006; Wang et al., 2011b). In addition to these guidance cues and mitogens, INs show a distinct and highly dynamic migration pattern, with one to many leading processes extending and branching during the migration cycle (Bellion et al., 2005; Godin et al., 2012; Gopal et al.,

2010; Lysko et al., 2011). Enhancement in CXCR4 signaling results in a simplified leading process and fast migration (Lysko et al., 2011). In contrast, a reduction in signaling leads to increased branching and a slowing of migration with more cells turning to invade the cortex, a process controlled by signaling through actin and MT dynamics (Lysko et al., 2011, 2014). Unlike radially migrating neurons, cortical INs grow new primary processes in order to turn into the cortex (Polleux et al., 2002). Finally, CGE derived INs, unlike MGE INs, require COUP-TFII (nuclear receptor and ligand inducible transcription factor) for normal tangential migration; however, further studies are required to understand the cellular mechanisms underlying this regulator (Kanatani et al., 2008; Tripodi et al., 2004).

Termination of migration

The termination of migration is also important for normal neuronal positioning and development. Relatively few studies have focused on this aspect of cell migration with most data focused on the termination of radial migration and the Reln pathway (also see below, *reeler* mouse). Mice mutant for the Reln receptor Vldlr show an increase in neurons invading the MZ as a result of failing to stop their migration (Hack et al., 2007). This is also consistent with observations in the ApoER2 mutant mouse in which excess neurons are also found at the top of the CP (Kubo et al., 2010). Reln induces the degradation of Dab1 via a proteasome-dependent system mediated by SOCS7-Cul5-Rbx2 to allow proper termination after neurons reach the top of the CP (Arnaud et al., 2003; Feng et al., 2007; Simo and Cooper, 2013; Simo et al., 2010). These results suggest that the Reln signaling pathway is involved in the termination of migration. Another molecule recently implicated in termination of migration is the actin regulator RhoA (see below, *RhoA* cKO mouse), although the mechanisms are less understood. Essentially no studies to date have identified molecules important for INs to stop migrating.

Birthdate-dependent organization and circuit formation in the cortex

Waves of successively generated pallial neurons migrate beyond earlier born neurons to form the CP, settling into layers in a birthdate-dependent, inside-out fashion (Fig. 1b, Gupta et al., 2002, Caviness et al., 2008). The result is the distinctive six-layer lamination of the neocortex. Pallial derivatives primarily give rise to excitatory, glutamatergic neurons, which will represent the majority (~80%) of neurons in the mature cortex. Clonally related neurons (i.e., those that are derived from the same progenitor cell) are thought to be distributed among all layers and exhibit specific connectivity (Gao et al., 2013). The situation may differ in the hippocampus, which exhibits one compact pyramidal cell layer with some clones giving rise to horizontally organized neurons (Xu et al., 2014).

Cortical neurons and INs born at the same time will eventually migrate into the same cortical layer despite different spatial origins and migration patterns (Campbell, 2005; Marin and Rubenstein, 2003). Heterochronic transplantation studies indicate that fate specification is a combination of intrinsic factors and extracellular signaling, and also that neuronal fate becomes progressively more restricted (Kriegstein and Noctor, 2004). Specifically, early-born progenitors can produce neurons with a layer (L) 2/3 cell fate when transplanted into a late environment, but late-born progenitors cannot produce L5/6 cells when transplanted into an early environment (reviewed in (Campbell, 2005; Kriegstein and Noctor, 2004). Similar

experiments using MGE progenitors, however, demonstrated that late-born progenitors have the potential to produce L5/6 INs when introduced into an early environment, in contrast to pallial progenitors (Valcanis and Tan, 2003). More recently, it was shown that projection neurons have the ability to influence the laminar fate of INs (Lodato et al., 2011), which likely contributes to the abnormal positioning of INs in malformed brains and recruitment of INs into SBH in some cases. Furthermore, signaling downstream of electrical activity may further refine genetic programming, even at the early developmental stages of proliferation and migration (De Marco Garcia et al., 2011; Spitzer, 2006).

Pallial-derived glutamatergic projection neurons settle in L2–6, with layer specific connectivity, and morphological and physiological characteristics (Gao et al., 2013; Molyneaux et al., 2007). In general, thalamic inputs target L4 neurons, which project to callosal projection neurons in L2/3 cells, which then send axon collaterals to L5/6 cells and also via the corpus callosum to L2/3 cells in the opposite hemisphere. L5/6 cells are primarily corticofugal projection neurons (with some callosal projections), sending information to subcortical structures. In addition to this canonical circuit model, studies in cat and monkey cortices provide evidence of radially organized cortical columns that interconnect neurons across layers to form a functional unit. Studies in rodents provide less robust evidence, perhaps due to the decreased number of cortical neurons, and possibly due to smaller sets of clonally related neurons (Gao et al., 2013). However, lineage tracing studies in mice do provide evidence that clonally-related neurons derived from the same RG cell, spanning multiple cortical layers, form the anatomical basis of functional columns (Li et al., 2012; Ohtsuki et al., 2012; Yu et al., 2009). Sister cortical neurons are preferentially connected by transient electrical synapses in early postnatal stages, and then chemical synapses at later stages (Yu et al., 2012).

Clonal analysis in the mouse hippocampus revealed that sister neurons rarely form synapses with each other, differing from the neocortex (Xu et al., 2014), but they tend to be commonly innervated by the same fast-spiking IN. This study also demonstrated that sister neurons tend to cluster horizontally starting in late development (Fig. 1), a finding that appears to conflict with inside-out lamination because sister neurons in the same “layer” are born on different dates. However, it is clear that the pyramidal layer in the hippocampus is vastly more compact than the CP in the neocortex. It is possible that both types of radial and horizontal organization exist simultaneously, and perhaps contribute to different functions. Another feature of birthdate-specific circuit formation occurs in the tri-synaptic circuit, with preferential connections between dentate granule cells, CA3 neurons and CA1 neurons born on the same date (Deguchi et al., 2011). Hippocampal pyramidal neurons are also morphologically and physiologically diverse, with a sub-population of the earliest-born neurons potentially serving as excitatory hub neurons in CA3 (Marissal et al., 2012). CA3 pyramidal neurons also differ from CA2 and CA1 neurons.

Cortical INs are much more diverse compared to pyramidal neurons of the cortex and hippocampus. In addition to stereotypic laminar positions, morphology and gene expression, they have local projections with sub-type specific synaptic connectivity patterns (Bartolini et al., 2013; Fishell and Rudy, 2011). Lineage tracing studies demonstrate that clonally related MGE or CGE derived INs form spatially isolated clusters in the neocortex (Brown et al.,

2011; Ciceri et al., 2013). Analysis of IN markers suggests that GE progenitors are capable of making more than one sub-type of IN (Sultan et al., 2014), although other studies suggest that different progenitor lineages produce INs destined for deep or superficial cortical layers (Ciceri et al., 2013). Future studies elucidating the details of IN development may be important to understand their critical role in regulating excitation and setting cortical rhythms (Marin, 2012).

Gliogenesis

Deficits in white matter are a common hallmark of neurodevelopmental disorders in rodent models and in humans (Fields, 2008), which is not surprising given the critical roles of glia in regulation of synapses, blood vessels and myelination. Like neurons, glial cells have also increased in diversity and number throughout brain evolution, suggesting their particular importance in the highly complex human brain (Freeman and Rowitch, 2013). Two main types of brain-derived glia, astrocytes and oligodendrocytes, are produced by progenitors both pre- and postnatally. The third major type of glia, microglia, is a specialized type of macrophage derived from the yolk sac (Nayak et al., 2014), and is therefore not discussed here. Early-born astrocytes (E12) can arise from the direct transformation of RG cells into glial progenitors, which then migrate by somal translocation into the preplate, and differentiate (Tabata, 2015). However, recent studies suggest that most glia are produced late in development from progenitors that are initially neurogenic (Fig. 1b; (Gao et al., 2014; Siddiqi et al., 2014). Postnatally, the number of astrocytes rapidly increases, which is due to the proliferation of intermediate astrocyte progenitors (Freeman and Rowitch, 2013) and/or the astrocytes themselves (Tabata, 2015). Oligodendrocytes are derived from regionally diverse populations of oligodendrocyte precursor cells (OPCs) that arise from progenitors during late gestation (Fig. 1b; (Bercury and Macklin, 2015). Cortical astrocytes and oligodendrocytes are also produced postnatally from the SVZ, from which glial precursors migrate dorsally into the grey and white matter and differentiate (Tabata, 2015).

Genes/pathways regulating neuronal migration: rodent models

In this section we discuss the functions of proteins having an influence on neuronal migration and we try to bring together useful mouse mutant data. We have divided this part up into different molecular functions. Figure 2 summarizes the major signaling pathways mentioned below in relation to their effects on the cytoskeleton. We resume the rodent model phenotypes in Tables 3 and 4 (omitting those that lack sufficient physiological and/or behavioral data, RNAi mouse models, IN models and type II lissencephaly models), and also in Figure 3, omitting pre- and perinatal lethal models.

Imperative role of the cytoskeleton during neuronal migration

Signaling pathways that induce morphological changes, final positions of migrating cells and even synaptogenesis are ultimately coordinated by downstream effects on the cytoskeleton. Extrinsic factors that modulate neuronal migration can come from secreted proteins (e.g. reelin from CR cells; (Frotscher, 1998), adhesive contacts with RG cells (e.g., connexins (Elias and Kriegstein, 2008; Hatten, 2002) and electrical activity even from very early stages of development (De Marco Garcia et al., 2011; Spitzer, 2006). Intrinsic factors

are related to birthdate specific gene expression, which may be initiated by changes in RG cells and proliferation dynamics over time (for review see (Kriegstein and Alvarez-Buylla, 2009; Pinto and Gotz, 2007). Understanding the dynamic nature of the cytoskeleton is key to understanding neuronal migration, and this has been emphasized by human genetics studies (Jaglin and Chelly, 2009; Poirier et al., 2013; Poirier et al., 2010).

Cytoskeletal components include MTs and actin filaments. MTs, composed of long polymers of alpha-beta tubulin dimers (Fig. 2), are constantly reorganizing in response to environmental and intrinsic cues. Inside the cell, this “dynamic instability” is regulated by MT assembly–promoting factors, stabilizing factors (such as MT-associated proteins (MAPs, e.g., DCX)), destabilizing factors, severing proteins, and motors of the kinesin and dynein superfamilies (Conde and Caceres, 2009). The selective stabilization (via post-translational modifications of tubulin) and bundling of MTs mediates cell polarization, migration and axon formation. Complex MT behaviors are required for growth cone advance, elongation, the growth of neuronal processes and recognition of guidance cues (Conde and Caceres, 2009).

Actin microfilaments are another important component of the cytoskeleton, and mutations in actin genes also result in MCD, as noted above. Actin polymerization is critical in leading processes to help guide migration (Lysko et al 2011, 2014). Some of these changes seem to be mediated by overlapping molecular pathways and master regulators such as LIS1 and CDK5 (Fig. 2, (Heng et al., 2010). Actin filament dynamics are also important for axon guidance with multiple functions in the growth cone where they exhibit reciprocal regulation with MTs (Arimura and Kaibuchi, 2007; Bradke and Dotti, 1999). Actin also plays an independent and important role in the trailing process during cell migration. For INs in particular, retraction of the trailing process functions to propel the nucleus forward. Non-muscle myosin II, coupled with actin filaments, is required for this process (Bellion et al., 2005; Schaar and McConnell, 2005). On the other hand, some key actin-regulating molecules may have more prominent roles in progenitors than neuronal migration *per se* (e.g., RhoA (Cappello et al., 2012). We dissect out specific aspects of these mechanisms in the following sections.

Tubulins

Disease-related human mutations in either TUBA1A or TUBB2B impair formation of tubulin heterodimers in *in vitro* assays, indicating that MT instability may underlie the end phenotypes (Jaglin et al., 2009; Keays et al., 2007). The *Tuba1a* mouse model (*Jna*^{-/-}), in the heterozygote state as for human mutations, shows lamination defects in the hippocampus and mild irregularities in L2–4 of the neocortex (Keays et al., 2007). Migration defects are also present in postnatally generated neurons in the dentate gyrus (Keays et al., 2010). Initial *in vivo* studies using RNAi targeting of *Tubb2b* in cortical progenitors of rats resulted in migration arrest of post-mitotic neurons in the SVZ/IZ (Jaglin et al., 2009). More recently the *Tubb2b* knockout (KO) mouse (brain dimple, *brdp*) was generated, which displays numerous brain malformations, increased apoptosis of progenitors and consequent thinning of the cortical epithelium (Stottmann et al., 2013). Although potentially different from the

human phenotype, this latter study confirms an important role for this gene in progenitors in the mouse, which may be different from the case of *Tuba1a*.

There are no studies reporting epileptic activity in any rodent model related to these genes, although they do display other behavioral abnormalities. *Tuba1a* heterozygotes (*Jna*^{-/-}) are hyperactive with impaired working memory and decreased anxiety, in fitting with altered hippocampal function (Keays et al., 2007). These mice also display an increased acoustic startle response, perhaps due to subtle structural abnormalities in the superior colliculus (Edwards et al., 2011). *Brdp* KO mice die shortly after birth, but *Brdp* (+/-) show hyperactivity like *Tuba1a* heterozygotes. Although humans with heterozygous *TUBB2B* mutations are quite severely affected, *Brdp* (+/-) mice appear to have normal lamination with only subtle changes in cortical gene expression, such as decreased *Gad67*, an IN marker (Stottmann et al., 2013).

Like TUBA1A, TUBB3/Tubb3 is apparently a neuronal-specific tubulin protein. In mice, *Tubb3* knockdown (KD) with shRNA leads to delayed bipolar morphology and radial migration, a phenotype that disappears postnatally (Saillour et al., 2014). It is interesting to note that BPs are apparently increased in this model, although this may be due to delayed neurogenesis. The transient nature of this mouse KD phenotype is unexpected compared to the human malformation. By contrast, *TUBB5* is the most highly expressed beta-tubulin in developing mouse and human brains, with high expression in neuroprogenitors. RNAi depletion of *Tubb5* in mice perturbs mitosis of progenitors and neuronal migration, perhaps due to impaired generation of polarity and leading processes (Breuss et al., 2012; Ngo et al., 2014). However, *Tubb5* is also essential for neuronal differentiation and dendritic spine formation *in vivo*, and is therefore also important post-mitotically (Ngo et al., 2014). There are no KO mouse models for either of these tubulins, and behavioral phenotypes of KD mice have not been reported.

As mentioned above, gamma-tubulins function in tubulin nucleation and are primarily found at centrosomes to support spindle formation (Kollman et al., 2011). Human mutations in *TUBG1* cause mitotic MT abnormalities *in vitro* (Poirier et al., 2013). *Tubg1* KO mice die at the blastocyst stage due to mitotic arrest (Yuba-Kubo et al., 2005); *Tubg1* KD leads to migration arrest in the SVZ/IZ, however the mechanisms are not yet clear (Poirier et al., 2013). Although *Tubg2* is almost exclusively expressed in the brain, the *Tubg2* KO has no apparent phenotype and cannot rescue *Tubg1* KO mice (Yuba-Kubo et al., 2005).

MT-interacting proteins: Lis1 and Dcx

The molecular functions of LIS1 and DCX have been described in numerous *in vitro* and *in vivo* studies (Friocourt et al., 2003; Kerjan and Gleeson, 2007; Xavier and Jaglin, 2009). These proteins may interact with each other and other MT-related proteins (Fig. 2), in some cases potentially compensating for each other functionally (Caspi M et al Hum Mol Genet 2000; Tanaka et al., 2004 J Cell Biol), although more severe phenotypes are observed in double mouse mutants (Pramparo T et al J Neuro 2010). LIS1 promotes length and stability of MTs by decreasing catastrophe (Sapir et al 1997), whereas DCX stabilizes MTs by enforcing their 13 protofilament architecture (Moores et al., 2004). However, there are important differences in these two proteins. *Lis1* is expressed in neuroepithelial progenitor

cells before the onset of neurogenesis, and continues to be expressed throughout adulthood (Yingling et al., 2008, Cell; Reiner et al., 1995 J Neurosci). *Dcx*, however, is expressed predominantly in post-mitotic neurons and is turned off after birth in mature neurons (P18 – P21, Kappeler et al., 2007).

Lis1 interacts with dynein, a MT motor known to transport cargo in the retrograde direction, Ndel1, which is required for centrosome duplication and mitotic spindle function, and Ndel1, a MT and dynein modulator (Fig. 2). Lis1 regulates nuclear migration in various cell types and organisms (Ayala et al., 2007; Conde and Caceres, 2009), and is required, along with dynein/Ndel1, for nuclear movement during neuronal migration by coupling the nucleus to the centrosome (Sasaki et al., 2005; Shu et al., 2004). Furthermore, the Lis1/dynein/Ndel1 complex regulates spindle orientation in mice, which is particularly important for symmetric division of neuroepithelial stem cells before neurogenesis to increase the progenitor pool. Decreased *Lis1* leads to apoptosis of neuroprogenitors, especially neuroepithelial stem cells that are apparently more sensitive to cleavage plane angle (Yingling et al., 2008). Other effects of *Lis1* downregulation include delayed neuronal polarization, changes in growth cone shape, and decreased MT bundling and axon formation (Ayala et al., 2007; Grabham et al., 2007; Tsai et al., 2005). *Dcx* has also been suggested to transiently affect proliferation in mice (Pramparo et al J. Neuroscience 2010; Yingling et al, Cell 2008), but is better known as a classical MAP that polymerizes and stabilizes MTs in post-mitotic neurons, albeit at a different binding domain than other structural MAPs such as MAP2 and tau (Moores et al 2004). *Dcx* is enriched at the ends of growing neurites, with roles in MT stabilization and axon formation in post-mitotic neurons (Conde and Caceres, 2009; Friocourt et al., 2003).

In mice (and presumably in humans), *Lis1* is indispensable for life; homozygous KO mice die prenatally (Hirotsume et al., 1998), and mice with *Lis1* ablation restricted to particular neuronal populations display massive brain deformations (Yingling et al., 2008). Mice with under (Hirotsume et al., 1998) and overexpression (Bi et al., 2009) of *Lis1* have similar brain abnormalities, demonstrating the importance of gene dosage. Unlike the drastic human phenotypes that affect the structure of numerous brain areas, *Lis1* heterozygote, similar to *Dcx* KO, mouse models display mild phenotypes with lamination defects primarily in the hippocampus, where several fragmented pyramidal cell layers are seen (Belvindrah et al., 2014, Table 3). Surprisingly, despite this, both models are useful for studying developmental epilepsy.

Interestingly, mutation of the *Lis1* allele in *C. elegans* causes deficits in GABA vesicle distribution and inducible seizures, which may be due to deficits in Lis1/dynein interactions (Williams et al., 2004). *Lis1* (+/–) mice (P14–26) have an increased number of glutamate containing vesicles in Schaffer collateral terminals that synapse onto CA1 pyramidal neurons (Greenwood et al., 2009). Increased spontaneous excitatory post-synaptic currents (sEPSCs) and miniature EPSCs (mEPSCs) recorded in the CA1 region, as well as increased paired pulse facilitation (PPF), are consistent with a larger pool of releasable glutamate vesicles (Greenwood et al., 2009). Field recordings also demonstrate enhanced excitability in CA1 (P28–60) with spontaneous epileptiform activity in high extracellular K⁺ occurring simultaneously in two heterotopic bands (Fleck et al., 2000). GABA transmission is also moderately increased in the CA1 (P14–22), with increased frequency and amplitude of

sIPSCs in CA1 pyramidal cells, and increased excitability of CA1 INs (Jones and Baraban, 2007). The origins of these physiological changes are unknown, but could be due to altered morphology of hippocampal neurons or defective synaptogenesis. Basal dendritic trees of CA1 pyramidal cells are less complex and shorter, whereas dentate granule cells are hypertrophic with the abnormal presence of spines on basal dendrites and somata (Fleck et al., 2000). *Lis1* has also been shown to regulate postsynaptic density mobility and organization of synaptic patterns on IN dendrites (Kawabata et al., 2012). Although it is still too early to bring these data together, the defects seem indicative of the abnormal functioning of the studied circuitry.

The study of *Dcx* mouse models is particular due to location of this gene on the X chromosome. Heterozygous females and hemizygous males have a similar anatomical phenotype, in each case the neocortex is normally laminated, although different severities in the extent of the bilayer formation of CA3 pyramidal neurons are observed (Corbo et al., 2002; Kappeler et al., 2007). There is a much larger difference in the phenotypic severity between male and female humans affected by *DCX* mutations, as discussed above. Hemizygous male mutant mice have been extensively compared physiologically, electrophysiologically and behaviorally to wild-types, although female *Dcx* heterozygotes were also shown to display abnormal behaviors (Corbo et al., 2002), and are likely to suffer from epilepsy (Nosten-Bertrand et al., 2008).

Despite a less widely affected pyramidal cell layer (CA1 is less affected in *Dcx* mutants), the morphological defects in *Dcx* (–/Y) mice are similar to *Lis1* (+/–), likely due to the underlying fact that both proteins influence MTs. CA3 pyramidal cells in *Dcx* (–/Y) mice have shorter dendrites and abnormal mossy fiber connectivity, with abnormally organized terminations on both apical and basal dendrites (Bazelot et al., 2012). These pyramidal neurons are also hyperexcitable (P21–35), and probably contribute to the increased susceptibility to epileptiform activity *in vitro* (Bazelot et al., 2012; Nosten-Bertrand et al., 2008). The exact mechanism underlying increased excitability in this model is also unknown. Potential roles for *Dcx* in the regulation of vesicles have also been suggested due to protein-protein interactions with AP1 and 2 (Friocourt et al., 2001), Kif11/VAMP (Liu et al., 2012) and the observation of perturbed axonal transport of vesicles in double *Dcx/Dclk1* KO mice (Deuel et al., 2006). The abnormal development of recurrent excitatory activity via excessive axon collaterals has also been proposed as an underlying mechanism for increased excitability (Bazelot et al., 2012), but this has not yet been shown anatomically. Developing neurons in *Dcx* KO mice have unstable and excessive branching on leading processes (Kappeler et al., 2006; Koizumi et al., 2006) and see below), likely due to impaired MT function and potentially also related to spinophilin, an interacting actin-bundling protein. Axonal tracing in adult hippocampal pyramidal neurons has not yet been performed to test if abnormal branching exists in differentiating neurons *in vivo* (Bielas et al., 2007).

Like *Lis1* (+/–) mice, *Dcx* (–/y) hippocampi also demonstrate increased inhibitory activity, with a greater frequency of sIPSCs in extracellular recordings (Bazelot et al., 2012; Jones and Baraban, 2007). It is possible that the increased inhibitory neurotransmission in both of these animal models is compensatory, or that it contributes to epileptogenesis in a

hyperexcitable brain, a speculation also for other epilepsy models (Chen et al., 2001; Walker and Kullmann, 1999).

In addition to the clear defects in radial migration, tangential migration of INs is also affected by loss of *Lis1* and *Dcx*. In humans with Miller-Dieker syndrome, there is a reduction in the number of INs in the developing cortex (Pancoast et al., 2005). This is also observed in *DCX* mutant post-mortem lissencephaly brains (Francis et al., 2006). To corroborate these findings, IN migration was studied in the *Lis1* mutant mouse line, which also revealed reduced IN migration speed, potentially impairing normal integration and functional circuit formation (McManus et al., 2004b). This was predominately a cell autonomous defect and included defects in leading process branching as noted earlier in this review (Gopal et al., 2010; McManus et al., 2004b; Nasrallah et al., 2006). Similar to *Lis1*, *Dcx* KO tangentially migrating neurons (embryonic from the GE and in the adult rostral migratory stream) also show similar morphological defects (Kappeler et al., 2006; Koizumi et al., 2006). KD of either *Dcx* or *Dclk1* (see also next subsection) in the GE results in a slowing but not a complete halting of migration (Friocourt et al., 2007). Interestingly, KD of *Dcx*, but not *Dclk1* (see also next subsection), also results in enhanced branching in migrating INs. This phenotype is reminiscent of blocking the *Cxcr4* pathway (Lysko et al., 2014), suggesting a possible crosstalk between *Dcx* and *Cxcr4* signaling.

Further similarities between *Lis1* and *Dcx* mutant mouse models exist at the behavioral level. *Lis1* (+/-) mice have certain learning and memory deficits as demonstrated in the Morris water maze, and impaired performance on the rotarod (Paylor et al., 1999). Some of these can be rescued by calpain inhibitors (Yamada et al., 2009). Many hippocampal-dependent behaviors are preserved in *Dcx* (-/Y) mice, including learning and memory function, but abnormalities in social behavior do occur (Germain et al., 2013). Importantly, both mouse models have spontaneous seizures as measured by video-EEG recording in *Dcx* mutants with indwelling cortical/hippocampal electrodes (Nosten-Bertrand et al., 2008) and *Lis1* mutants with scalp electrodes (Greenwood et al., 2009). In *Dcx* mutants, epileptic activity most likely starts in the hippocampus and then propagates to the cortex. Given that *Lis1* mutants also display the most severe lamination defects in the hippocampus, albeit equally among the CA fields, it would be interesting to investigate the origin of seizures in these mice as well.

The subtle neuronal migration phenotype of *Lis1* and *Dcx* KO mice has prompted other strategies to create models that have more severe MCD, as in human. Creating double KOs targeting similar genes can indicate function within the same molecular pathway, and often creates a more severe phenotype (for examples, see next subsection). Double KOs and acute KDs using RNAi may overcome compensation by other genes/proteins. RNAi can also be performed in organisms other than the mouse, providing species-specific advantages. Curiously, RNAi targeting of *Dcx* in rats but not in mice results in SBH, although neuronal migration is also disturbed in mice (Bai et al., 2003; Ramos et al., 2006). Like *Dcx* KO mice, *Dcx* KD rats show abnormal morphology of misplaced neurons; SBH but not normotopic cortical neurons have misoriented dendrites and also abnormal axon projections (Lapray et al., 2010). Adult *Dcx* KD rats also exhibit hyperactivity and spontaneous epilepsy (Lapray et al., 2010). Due to the harder rat skull, juvenile rats can be implanted with

permanent indwelling electrodes, which revealed that juvenile *Dcx* KD rats probably do not experience spontaneous seizures, although they are more sensitive to convulsants (Lapray et al., 2010). The size of the SBH was found to be variable related to the technique of introducing RNAi in the developing brain (*in utero* electroporation), which allowed the demonstration of a correlation between the severity of the spontaneous seizures and the size of the SBH, and also to age (Lapray et al., 2010). This resembles the situation in humans where the thickness of the SBH is correlated with the severity of the phenotype (Bahi-Buisson et al., 2013).

Electrophysiology studies revealed that the normotopic cortex that overlies the SBH in *Dcx* KD rats may contain the epileptic origin (Petit et al., 2014). This may be in line with other epilepsy models that also show abnormal properties of neurons surrounding the malformation (e.g., PVH, tuberous sclerosis, freeze-lesion models; see discussion). Studies in young rats (2 weeks) demonstrated a developmental delay of GABAergic synapses in heterotopic cortex (Ackman et al., 2009), perhaps leading to further circuit abnormalities underlying the epileptogenesis. The cause may be the abnormal environment of the heterotopia and/or the abnormal morphology of heterotopic pyramidal neurons (Lapray et al., 2010).

RNAi targeting of *Lis1* in rats at E16 also produces an SBH (Tsai et al., 2005), and furthermore revealed, perhaps more so than in the *Lis1* (+/−) mouse, that this protein has a prominent role in progenitors. Interkinetic nuclear migration and mitosis were abolished in affected progenitors, as was the multipolar to bipolar transition, resulting in arrested migration that formed the SBH. The morphological and physiological properties of these neurons and the epileptic status have not been investigated, but would provide an interesting comparison to *Dcx* KD rats and other SBH models.

MT-interacting proteins: *Dclk1&2*

Dclks, as well as having a kinase domain, have MT binding domains that are highly homologous to *Dcx*; however unlike *Dcx*, they are expressed in neurons of the adult mouse brain and during embryogenesis in progenitors (Shin et al., 2013). *In vitro*, *Dclks* are localized to the end of dendrites where they promote growth and suppress synapse maturation (Shin et al., 2013). *Dclk1* is expressed in several brain regions (Deuel et al., 2006), and in neuroprogenitors it plays an important role in mitotic spindle formation (Shu et al., 2006). *Dclk1* KO mice appear to have a normal phenotype, but *Dcx*(−/Y)/*Dclk1*(−/−) have severe, widespread brain malformations and disruption of white matter tracts, the phenotype hence being more reminiscent of human lissencephaly (Deuel et al., 2006). Unfortunately these mice die within a few days of birth and so cannot be investigated as an epilepsy model. Studies of cultured neurons deficient in both proteins (obtained from *in utero* electroporation studies with RNAi targeting) indicate deficits in dendrite and axon formation, as well as defective expression and localization of synaptic vesicle proteins.

Dcx(−/Y)/*Dclk2*(−/−) double mutants are also more severely affected than *Dcx*(−/Y), in terms of hippocampal lamination defects with early onset (~P21) epileptic seizures that may underlie their decreased post-weaning survival rate (Kerjan et al., 2009). Like *Dcx*(−/Y) mice, *Dcx*(−/Y)/*Dclk2*(−/−) mice have spontaneous seizures that start in the hippocampus,

with abnormal dendritic morphology seen in this region. Mossy fibers are also similarly affected in both models, although this could be a consequence of post-synaptic pyramidal cell defects. Calbindin hippocampal INs are mispositioned, with decreased frequency of sIPSCs detected in CA1 pyramidal neurons before seizure onset at P11. Decreased inhibitory tone in this model may differentiate it from *Lis1* (+/–) and *Dcx* KO models; however, it is difficult to make direct comparisons due to different ages of the mice in each of the three studies. Although MCD patients with *DCLK* mutations have not been identified, *Dcx*(–/Y)/*Dclk2*(–/–) mice are perhaps an attractive model for further studying neurodevelopmental epilepsy due to their robust morphological and early-onset behavioral phenotype.

Other MT-related proteins

-MAPs—The Map2/Tau family of proteins stabilize MTs, and share functional redundancy with Map1b as revealed in double KO mice (Dehmelt and Halpain, 2004). *Map2* KO mice appear normal, but *Map2/Map1b* double KO mice have abnormalities in several brain regions (Teng et al., 2001). In addition to fiber tract abnormalities, neuronal migration is impaired, causing disrupted lamination in the hippocampus, olfactory bulb, cerebellum and cortex, although inside-out birthdate positioning was preserved in the latter (Teng et al., 2001). The molecular cause of disrupted MT organization, was observed in cultures of primary hippocampal neurons from these mice.

Similar results were obtained with *Map1b* and *Tau*; *Map1b* KO mice have commissural deficits and disturbed laminar organization in the hippocampus, with more severe phenotypes in double KOs (Takei et al., 2000). Another *Map1b* mutant pinpoints the role of this protein in peripheral axon guidance and myelination as well (Meixner et al., 2000). Similar to *Map2/Map1b* double KO mouse studies, hippocampal and cerebellar primary neuron cultures from *Map1b/Tau* double KOs demonstrated MT disorganization, impaired neurite outgrowth and migration delays (Takei et al., 2000). Little has been reported about the behavior of any of these mouse mutants as they tend to die perinatally.

-Kinesins—Patients with MCD and mutations in the above mentioned structural MAPs have not been reported, although other MT motor proteins have been, including KIF2A, DYNC1H1 and KIF5C (Poirier et al., 2013). KIF2A, a member of the kinesin 13 family, is a plus-end molecular motor that regulates axonal collateral branching via ATP-dependent depolymerization (Conde and Caceres, 2009). *Kif2a* KO mice have aberrant axonal growth, with axon collateral branching and decreased MT depolymerization (Homma et al., 2003). Abnormal lamination is apparent in all laminar structures including the cortex, hippocampus and cerebellum, and there is also an absence of brainstem and cerebellar nuclei. Delayed migration was confirmed by BrdU birthdating (Homma et al., 2003). Loss of *Kif2a* is perinatal lethal; a conditional KO (cKO) could hence be a useful model, as was the case in some of the following studies.

Kif5C is a neuronal kinesin that is highly expressed in motor neurons in a developmental manner, and KO mice display motor neuron loss and a minor reduction in brain size (Kanai et al., 2000). Using a mutant KIF5C construct based on an MCD patient mutation associated

with epilepsy and ID, transfected primary hippocampal neurons demonstrated altered KIF5C localization and decreased mEPSCs, implicating a role for this protein in trafficking glutamate receptors (Willemsen et al., 2014). Another neuronal specific KIF, *Kif5a*, leads to an epilepsy phenotype in cKO mice in which synapsin-Cre restricts loss of Kif5A postnatally (Nakajima et al., 2012). As a result of inactivation after neuronal migration has been completed, there are no histological brain abnormalities, although mice die around P21 (perhaps due to growth abnormalities and/or epilepsy). An important discovery of this study was the regulation of GABA_AR surface expression by Kif5A. Physiological effects include decreased mIPSC amplitude in CA1 pyramidal neurons, decreased ratio of evoked IPSCs/EPSCs, and decreased EEG power (Nakajima et al., 2012).

-Cdk5 and p35—Human genetic mutations in *CDK5* and *p35* have not been reported, but corresponding mouse models have useful molecular and behavioral phenotypes for the study of neurodevelopmental epilepsies. CDK5 is a non-receptor kinase that phosphorylates many components of the cytoskeleton including neurofilaments, MAPs and actin regulatory proteins that are important regulators of neuronal migration and neurite outgrowth (Su and Tsai, 2011). *Cdk5* KO mice have severe neuronal migration and positioning defects in the cerebellum, hippocampus and neocortex, with an inversion of inside-out layering in the latter; like other mice with severe structural abnormalities, they die pre- or perinatally (Ohshima et al., 1996). To circumvent this problem, a forebrain specific cKO was generated by crossing with CamKII-Cre mice (Takahashi et al., 2010). *Cdk5* cKOs have the same forebrain phenotype as constitutive KOs, with inverted cortical layering and a disrupted hippocampal pyramidal cell layer, and they develop spontaneous seizures by two months of age. Additionally, these mice display progressive neurodegeneration from E18.5, either a cause or consequence of the observed brain inflammatory response.

Mutation of p35, a neuronal-specific kinase that activates CDK5 (Tsai et al., 1994), yields a mouse model with a similar phenotype. p35 is expressed in post-mitotic neurons, not progenitors, and is maintained at high levels only in the forebrain of adult rodents (Delalle et al., 1997). *p35* KO mice have lamination defects in several structures including the neocortex, hippocampus, cerebellum and olfactory bulbs, and additionally have enlarged ventricles (Chae et al., 1997). The morphology of cortical pyramidal cells was also abnormal, with incorrect orientation of somata and dendrites. The hippocampus was relatively less affected, having a less diffusely packed pyramidal layer; heterotopic granule cells in the dentate gyrus were also identified, with abnormal dendrites, and mossy fiber axons showing recurrent sprouting (Wenzel et al., 2001). Granule cells are not intrinsically hyperexcitable as shown by intracellular recording, but antidromic stimulation of mossy fibers led to functional evidence of recurrent axonal projections (Patel et al., 2004). In addition to increased susceptibility to chemically induced seizures, mutant mice die from 3 weeks of age possibly due to spontaneous seizures (Chae et al., 1997), confirmed in adult mice (three months old) using video-EEG monitoring (Wenzel et al., 2001).

A possible mechanism of perturbed inside-out layering is altered RG cell-neuron contact, which leads to an altered mode of migration. In neocortical slices from *p35* KO mice as early as E13, post-mitotic neurons demonstrated branched migration instead of somal translocation and/or normal RG cell guided locomotion (Gupta et al., 2003). This altered

migration (described as a zig-zag motion), likely leading to lowered probability of attachment to a single RG process, seems to have some similarities with the climbing mode previously described in the hippocampus. However, neurons from *Dab1* deficient mice (reelin pathway, see below) rarely displayed this mode of migration, even though these mice have a similarly inverted cortical layering (Gupta et al., 2003), suggesting multiple mechanisms can lead to this phenotype.

Extracellular signals

The most studied extracellular signal affecting neuronal migration is reelin, a large glycoprotein secreted during development by CR cells located in the MZ. Also, a subset of INs expresses reelin postnatally (Fishell and Rudy, 2011). *Reln* mutant mice (*reeler*) have numerous brain malformations resembling the human *RELN* mutation phenotype (Guerrini and Parrini, 2010), including lamination defects in the neocortex, hippocampus and cerebellum, in which there is hypoplasia and also a lack of foliation. In the cerebellum, granule cells that have migrated tangentially from the rhombic lip normally express reelin, which may serve as an attractant for radially migrating Purkinje cells (D'Arcangelo and Curran, 1998). *Reeler* mouse Purkinje cells do not migrate into the cerebellar cortex, and there are reduced numbers of both Purkinje and granule cells. In the neocortex, the *reeler* phenotype is often described as a “partial inversion” of layers due to failure of preplate splitting as well as the failure of late-born neurons to migrate past early-born neurons. Recent data using several layer-specific markers suggests a “mirror-image” laminar architecture in which layer 2/3 neurons are in the middle of the cortex with layer 4/5/6 neurons displaced above and below (Boyle et al., 2011), and furthermore differences among cortical areas were revealed. In the hippocampal CA fields, pyramidal cells are sorted into 2 or more distinct layers according to birthdate, and again there is an inversion of birthdate-dependent lamination. DG granule cells, which are mainly produced from late embryonic stages through adulthood, are also dispersed, and their dendrites project randomly in all directions instead of being uniformly directed toward the MZ (Frotscher, 2010). Surprisingly, reelin plays a role in maintaining a compact DG granule cell layer even in adult animals; disruption of reelin signaling via reelin antibody or kainate injection causes dispersion of mature, but not newborn, granule cells (Heinrich et al., 2006). Granule cell dispersion has also been identified in humans with epilepsy and in other rodent epilepsy models (Sloviter et al., 2012).

Reelin signaling pathways are well described, with activation of lipoprotein receptors (VLDLR and ApoER2) activating Dab1, PI3K, Notch, Fyn/Src and cofilin intracellular cascades that lead to modifications of the cytoskeleton (Belvindrah et al., 2014; Folsom and Fatemi, 2013; Frotscher, 2010), and mice with mutations in *Vldlr*, *ApoEr2* and *Dab1* phenocopy *reeler* mutants. Despite numerous studies there is no clear consensus as to the exact role of reelin in brain development, although there are likely several roles that are both cell autonomous and extrinsic, acting at different stages of migration (Belvindrah et al., 2014; Bozzi et al., 2012; Frotscher, 2010). The cause of migration defects may be due to the instability and misorientation of the leading process of migrating neurons in the absence of reelin, perhaps due to lack of stabilization of the actin cytoskeleton; indeed, normal stabilization of the actin cytoskeleton may be a stop signal (Frotscher, 2010; Olson et al.,

2006). Some neurons over-migrate into the MZ, further implicating reelin as a stop signal (Hack et al., 2007; Trommsdorff et al., 1999). Ablation of *Dab1* in post-mitotic neurons prevents glial-independent somal translocation of early-born neurons and terminal somal translocation in late-born neurons (Franco et al., 2011), confirming the role of reelin signaling in this process. Finally, reelin may also cause detachment of the migrating neuron from the RG fiber (Dulabon et al., 2000; Sanada et al., 2004).

Given the widespread malformations in *reeler* mice, particularly the dispersion of granule cells that is associated with mesial temporal lobe epilepsy in humans (Sloviter et al., 2012), it is surprising that they do not appear to exhibit spontaneous seizures. Adult (3–7 month) homozygotes do however, have increased susceptibility to electroshock-induced (Patrylo et al., 2006) and anesthesia-induced seizures (Kopjas et al., 2006). *Reeler* homozygous mutants (> 2 weeks) also demonstrate ataxia and an abnormal gait, likely due to their cerebellar defects (D'Arcangelo and Curran, 1998).

The movement disorder of *reeler* homozygotes confounds their use in behavioral studies; hence, heterozygotes have been used especially to evaluate the potential use of these mice as a model for psychiatric diseases. Interest stems from human genetic studies linking *RELN* mutations to cognitive disorders, particularly schizophrenia (Impagnatiello et al., 1998), and also studies showing that schizophrenic patients have decreased levels of reelin in postmortem brains (Guidotti et al., 2000; Impagnatiello et al., 1998). Results are variable with some studies reporting no behavioral differences between adult heterozygous *reeler* mice and WT littermates (Podhorna and Didriksen, 2004; Salinger et al., 2003; Teixeira et al., 2011) with others showing deficits (Brigman et al., 2006; Larson et al., 2003; Qiu et al., 2006; Rogers et al., 2013; Tueting et al., 1999; Weeber et al., 2002). Two studies report decreased pre-pulse inhibition in adult *reeler* (+/–) mice (Tueting et al., 1999; Qiu et al., 2006), a behavioral test of sensorimotor gating that is also highly associated with schizophrenia in patients (Kumari and Sharma, 2002).

Physiology reports in *reeler* heterozygotes are also quite variable, but abnormalities in CA1 appear common. Reelin enhances tetanus-induced long-term potentiation (Weeber et al., 2002), and both long-term potentiation and long-term depression are impaired in mutants (Qiu et al., 2006), perhaps due to reelin's interactions with many post-synaptic density proteins including glutamate receptors (Folsom and Fatemi, 2013). Heterozygotes also have decreased expression of GAD67, an interneuron marker, in several layers of frontoparietal cortex (Liu et al., 2001). Studies in homozygotes suggest deficits in inhibitory tone; spontaneous epileptiform activity was observed *in vitro* in the presence of a GABA_A receptor antagonist in neocortical and CA1 slices (Patrylo et al., 2006). *In vitro* neocortical extracellular recordings revealed decreased paired-pulse inhibition (10 ms interval) and paired-pulse facilitation (50 ms interval) (Patrylo et al., 2006), also suggesting changes in presynaptic vesicular release, although further studies are needed to implicate a pre- or postsynaptic mechanism.

A recent study provides more concrete evidence for reelin's role in neurotransmission. An increased number of vesicles was observed in CA1 of *reeler* homozygotes, as was decreased paired-pulse facilitation (Hellwig et al., 2011). A component of the vesicle release

machinery, SNAP25, was found to be downregulated, and addition of reelin to brain slices *in vitro* rescued these deficits. A role for reelin in spinogenesis is also apparent, as *reeler* heterozygotes show decreased spine density in CA1 (Liu et al., 2001) whereas adult mice that overexpress reelin have spine hypertrophy (Pujadas et al., 2010). These studies hence show multiple potential roles for reelin, which can perhaps be further clarified in the future.

Interneuron models

As mentioned previously, experimental models, predominately murine, of human migration disorders such as the lissencephalies, have all shown deficits in the migration of INs. For example, the *Lis1* (+/−) mouse shows cell autonomous IN migration defects (McManus et al., 2004b). The *Arx* (−/Y) mouse also shows an IN migration deficit, although in this case the defect appears to be not an inherent migration problem, but rather a failure of INs to recognize appropriate cues or targets directing them to turn and migrate into the cortex from their normal tangential migration (Marcorelles et al., 2010). Similarly, abrogation of *Dcx* in INs also results in a slowed migration and moderate increase in the branching of the leading process (Friocourt et al., 2007; Kappeler et al., 2006; Koizumi et al., 2006). Patients with mutations in *LIS1*, *ARX* and *DCX*, like the mouse models, show defects in IN distribution but they too are different from each other suggesting each of these genes plays a unique role in IN migration (Marcorelles et al., 2010).

More generally, studies in animal models with IN defects can categorize proteins into discrete functions. The migration of INs from the ventral forebrain requires guidance factors (e.g., Ephrin/Ephs, Netrin1 and integrins, Sema3a/neuropilin2, Slit/Robos, CXCL12/CXCR4, and TAG1), growth factors (e.g., GDNF, BDNF/NT4/TrkB, HGF-SF, Neuregulin/ErbB4), neurotransmitters (e.g., GABA, glutamate), transcription factors (e.g., COUP-TFII, *Dlx*'s, *Arx*, *Lhx6*), and other signaling and structure proteins (e.g., Rac1, Cdk5, Connexin-43, Kcc2, *Dcx*, and *Lis1*; see table 20–1 (Petros and Anderson, 2013). These animal models have clarified many characteristics of IN locomotion, guidance and positional information.

Importantly, behavioral studies in many of these models have clearly identified a direct relationship between IN migrational defects and epilepsy and other neuropsychiatric disorders. The first *Arx* mouse model, a KO, displayed forebrain and testes malformations that resembled human XLAG, but was perinatal lethal (Kitamura et al., 2002). In an *Arx* cKO model that selectively targets INs, mice display no obvious brain malformations but develop seizures starting by P14 (Marsh et al., 2009). Furthermore, it was shown that mutations in patients that do not alter gross brain structure, such as an expansion in an alanine tract within *ARX*, result in defects that affect INs but not projection neurons in the corresponding mouse models (Kitamura et al., 2009; Nasrallah et al., 2012; Price et al., 2009). These models each display an epilepsy phenotype (see Table 1 (Olivetti and Noebels, 2012).

The *Dlx* family of transcription factors also regulate migration and differentiation of INs (Panganiban and Rubenstein, 2002). *Dlx1/2* double KO mice show a massive deficit of tangential migration of subpallial INs (Anderson et al., 1997). In *Dlx1* KO mice, INs migrate normally but an age-dependent loss (via apoptosis) of NPY, somatostatin and calretinin

positive neurons starting at ~P30 was reported (Cobos et al., 2005). This was accompanied by a decrease in sIPSC frequency and amplitude in neocortex L2/3 and CA3 pyramidal neurons. Stress-induced seizures were observed in adults (2 months), and spontaneous seizures were observed during EEG recording (6–10 months) (Cobos et al., 2005). Other behavioral abnormalities of *Dlx1* KO mice include hyperactivity and impaired fear conditioning (Mao et al., 2009). Interestingly, CA1 INs in brain slices from young mice (P9–12) displayed properties suggesting delayed maturation compared to WT, potentially causing a compensatory decrease in glutamatergic drive onto CA1 pyramidal cells, which is apparent at P30 (Jones et al., 2011). The cause of delayed IN maturation is unknown, but could be related to reduced dendrite branching and length that limits synaptic input (Cobos et al., 2005), and therefore the involvement of proteins regulating the cytoskeleton. Although the *Dlx1* KO mouse does not display an MCD-like gross brain phenotype, it is a useful model for studying developmental epilepsy, and the progression of circuit dysfunction will be interesting to compare to other MCD models. In particular, the delay in IN maturation is reminiscent of findings in the heterotopic cortex in the *Dcx* KD rat (Ackman et al., 2009).

SBH rodent models

In addition to the *Dcx* and *Lis1* RNAi rat models mentioned previously, there are germline genetic rodent models for SBH. The mutation underlying the heterotopic cortex *HeCo* mouse phenotype was recently identified as the *Eml1* gene, which codes for a MT-binding protein that is expressed in neuroprogenitors and post-mitotic neurons (Kielar et al., 2014). Despite the fact that Eml1 binds to MTs, *Eml1* inactivation did not alter neuronal migration in brain slices *in vitro*. Instead, a perturbation of neuroprogenitors was observed, which are misplaced (ectopic) outside of the VZ/SVZ. Eml1 localizes to the mitotic spindle, which shows abnormal orientations in *HeCo* mouse progenitors, potentially leading to the detachment of some progenitors from the apical membrane. The resulting bilateral SBH is therefore more likely a result of misplaced proliferating progenitors whose progeny may form a physical barrier for migrating neurons, rather than a cell-autonomous migration defect.

HeCo mice show variability in the extent of heterotopia, enlargement of ventricles, body weight/size, and sometimes also possess cranial malformations and hypokinesia (Croquelois et al., 2009). Initial histological analysis and BrdU birthdating showed that cells in the postnatal SBH are late-born, and there are less of these cells in the normal overlying cortex (Croquelois et al., 2009). However, subsequent studies at earlier developmental time points demonstrated that early-born neurons also become “stuck” temporarily in the heterotopia, although they eventually manage to migrate to their normal positions in deep layers of the normocortex (Kielar et al., 2014). Myoclonic jerks in 4–5 week old animals were seen during behavioral observations, and adult *HeCo* mice (12–16 weeks) have increased susceptibility to induced seizures *in vivo* (Croquelois et al., 2009). Hyperexcitability has not yet been investigated with electrophysiological recordings to compare the normal and heterotopic cortices, although the reported contralateral normocortex projections to the SBH could provide the means of synchronous activity underlying seizure susceptibility (Croquelois et al., 2009).

Another SBH model is the *Tish* rat, which like the *HeCo* mouse, arose spontaneously, in this case from a mutation that has not yet been identified. The heterotopic cortex has abnormal lamination and orientation of apical dendrites, whereas the normotopic cortex, although reduced in size, has normal lamination and radial dendritic orientation (Lee et al., 1997). Early born cells are located around the rim of the heterotopia, with later born cells in the center, potentially differentiating this model from the mouse *HeCo* phenotype (Lee et al., 1998; Schottler et al., 1998). Adult rats have spontaneous seizures with seemingly simultaneous activity of normotopic and heterotopic cortices, although *in vitro* experiments suggest that the normotopic cortex is more prone to epileptic activity (Chen et al., 2000), as was the case in the *Dcx* KD rat (Petit et al., 2014). The causes of seizure activity are still under investigation, although inhibitory neurotransmission appears to be compromised *in vitro*. There is decreased frequency of sIPSCs and mIPSCs in layer 5 pyramidal neurons from both normotopic and heterotopic cortices compared to WT at P15, before seizure onset, which may be caused by a decreased density of PV+ INs in both cortical areas (Trotter et al., 2006),

The neuronal migration defect in *Tish* rats appears to be secondary to progenitor defects. Some mitotically active RG cells and BP cells are misplaced outside of the VZ/SVZ, mirroring the phenotype of the *HeCo* mouse (Fitzgerald et al., 2011). Heterotopic progenitors have increased cell cycle kinetics, with increased proliferation and compensatory apoptosis. Properly located progenitors in the VZ/SVZ contribute to normal and heterotopic cortex (Fitzgerald et al., 2011), raising the question as to whether there is a cell-intrinsic migration problem, or whether the developing heterotopia serves as a physical barrier, as hypothesized in *HeCo* mouse. However, the birthdate identities and layering of the SBH in these models is quite different, perhaps suggesting different mechanisms underlying the SBH formation, or species differences.

Another SBH model with a concentric birthdate organization in the heterotopic cortex is the *RhoA* cKO in which *Emx1*-Cre restricts recombination to the cortex after E12 (Cappello et al., 2012). As in all SBH models, there is normal lamination in the normotopic cortex, and also a greater number of later born neurons in the SBH. A unique feature of this model is the evidence of over-migration, with patches of basement membrane disruption resembling cobblestone lissencephaly (Cappello et al., 2012). Surprisingly, axon and dendrite polarity is normal in both the normocortex and SBH. Loss of adherens junction anchoring at the apical surface appears to underlie the ectopic position of progenitors, which are found scattered after E12. Also as in the previous models, radial processes are moderately misaligned, potentially further deterring RG cell guided locomotion. RNAi experiments demonstrated that RhoA-depleted neurons migrated even faster than controls, providing a possible explanation for the cobblestone phenotype and also implicating RhoA as a negative regulator or stop signal during migration. Physiological and behavioral phenotypes of *RhoA* cKO mice have not been reported.

Small GTPases like RhoA and Rap1 are regulated by guanine nucleotide exchange factors (GEFs), which are each associated with neurite outgrowth, and cell-cell and cell-matrix adhesions. cKO mice with ablation of *RapGEF2* restricted to dorsal telencephalon (via *Emx1*-cre) causes a massive bilateral SBH that contains randomly arranged neurons that

were presumably destined for all cortical layers (Bilasy et al., 2009). Again, the overlying cortex is thinner but correctly laminated. These mice have increased susceptibility to induced seizures at 9–12 weeks old (Bilasy et al., 2009). RNAi targeting *RapGEF2* *in utero* also causes SBH in adult animals, with abnormal dendritic arbors on ectopic neurons, as well as white matter agenesis (Ye et al., 2014). This protein, activated by CDK5, was shown to play a role in the multipolar to bipolar transition in the IZ, leading to downstream activation of Rap1/N-cadherin. Unlike other proteins posited to regulate this transition, *RapGEF2* is specifically expressed in neurons in the IZ where they change migration mode/morphology (Ye et al., 2014). Interestingly, unlike many of the SBH models described above, ectopic progenitors were not reported in either of the *RapGEF2* studies.

PVH models

Filamin 1 (FLNA) is an actin crosslinking protein that serves as a scaffold to link extracellular signals with diverse intracellular signaling cascades including the Rho and Ras families of GTPases (Fig. 2), which also have confirmed roles in neuronal migration via regulation of actin-MT interactions (Conde and Caceres, 2009; Sheen, 2014). *FlnA* is developmentally regulated with high expression during periods of neuronal migration in humans and rodents, and diminished expression thereafter (Carabalona et al., 2012; Fox et al., 1998). This protein may play a role in both progenitor organization and migrating pyramidal cells (Feng et al., 2006). The human heterotopia was shown to be composed of late-born neurons that failed to migrate away from the ventricle surface (Sheen, 2014). The ventricular surface was shown to be disrupted in both *FlnA* KO mice (Feng et al., 2006), which were embryonic lethal due to cardiovascular defects, and in *FlnA* KD (E15) rats (Carabalona et al., 2012). In the latter study, the apical attachment of RG cells was impaired, as was cell cycle progression, phenotypes which presumably precede and cause subsequent neuronal migration defects and the PVH phenotype, involving both early and later-born neurons in the rat. By contrast, neither of the two *FlnA* mutant mouse lines showed evidence of heterotopia (Feng et al., 2006; Hart et al., 2006). *FlnA* KD rats at P30 were more sensitive to chemical convulsants, although unlike *Dcx* KD rats (Petit et al., 2014), there was no correlation between the extent of the brain malformation and seizure susceptibility. Humans with PVH show seizure activity either originating in overlying cortex (which is often dysplastic) or arising simultaneously in the cortex and ectopic nodules (Scherer et al., 2005; Tassi et al., 2005). Therefore, it would be interesting to see physiology studies in *FlnA* KD rats analogous to those performed in *Dcx* KD rats that implicated normotopic cortex as the origin of epileptic activity (Petit et al., 2014).

Mutation of genes related to *FlnA* appear to serve as better PVH mouse models than *FlnA* itself, producing defects similar to *FlnA* KD rats. Loss of mitogen-activated protein kinase kinase 4 (MEKK4) in KO mice (or by RNAi), a regulator of *FlnA* phosphorylation, produces impaired neuronal migration, large breaches in the ependymal lining and PVH formed mainly by early to mid-born (*Tbr1*+) neurons (Sarkisian et al., 2006). Subpial ectopias were also observed in some KO brains, as was exencephaly and degeneration due to apoptosis. A second human PVH gene, *ARFGEF2*, coding for brefeldin-A-inhibited guanine exchange factor-2 (BIG2) promotes FLNA phosphorylation, and is likely to play a role in endocytosis, regulating levels of Arf1 at the plasma membrane, which is known to influence

cell-cell contacts (Zhang et al., 2013). Some *Big2* KO mice developed exencephaly, abnormal positioning of cells at the ventricular surface, heterotopia in ventricular regions and perturbed neuronal migration (Zhang et al., 2012). PVH was also induced by KD of *C6orf70* in the developing rat cortex, a gene of unknown function, mutated in a PVH patient, which codes for a protein with a vesicle-like subcellular localization (Conti et al., 2013). KD (E13.5) of either *Dchs1* or *Fat4*, genes found to be mutated in a human syndrome that includes several characteristics including PVH, results in progenitor defects, migration defects and heterotopia (Cappello et al., 2013). These two proteins are protocadherins that form an adhesive receptor-ligand complex located at the apical neuroependymal surface (Cappello et al., 2013). Together, these studies underline the importance of maintaining integrity of the neuroependymal surface for both progenitor function and neuronal migration. KD studies of genes such as these generally have not yet generated further study of the consequences of rodent PVH at later stages.

Neuronal over-migration and PMG mouse models

We mention briefly here the few models we know of concerning type II lissencephaly and PMG, which are overlapping entities. Genes related to type I lissencephaly have the common characteristic of inhibiting neuronal migration, but it seems to be a lot less clear how and why neurons over-migrate due to breakages in the overlying basement membrane (BM). Few mouse models are available to study type II lissencephaly related to glycosylation genes, likely due to the additional role of these genes in also regulating muscle integrity. KO of *Pomt1* or *Pomt2* is embryonic lethal (Hu et al., 2011; Willer et al., 2004), but *Pomt2* cKO (Emx-Cre) mice display lamination problems in the neocortex and hippocampus (Hu et al., 2011). Surprisingly neurons did not overmigrate beyond layer 1 despite breaches in the BM, although there was abnormal fusion of the two cerebral hemispheres. Two KO mouse models of muscle-eye-brain-disease with ablation of *Large* (Holzfeind et al., 2002) or *Pomgnt* (Liu et al., 2006) have similar phenotypes with additional deficits in the cerebellum.

Mechanisms involved in PMG in particular seem to represent a current stage of active research in mouse models (see (Bizzotto and Francis, 2015)). Similar to type II lissencephaly, key mechanisms so far appear to be related to disruption of the BM, detachment of RG cells at the basal surface, and/or problems related to CR cells (Bizzotto and Francis, 2015). For example, *Gpr56* KO mice show breaches in the BM, leading to an over-migration phenotype (Li et al., 2008) see also (Bahi-Buisson et al., 2010). *Col3a1* KO mice show a similar phenotype (Jeong et al., 2012), Col3a1 also being a major constituent of the BM. Further work is required to dissect out these constituents.

PMG rodent models have also been generated by mechanical non-genetic approaches, such as freeze lesioning performed in the postnatal period, which leads to the formation of local microgyri e.g., (Peters et al., 2004; Redecker et al., 2000). This latter model represents an interesting environmental approach which can also be combined in the future with genetic models.

Discussion

Neuronal migration disorders of the type 1 lissencephaly spectrum (agyria/pachygyria/SBH) are grouped together based on MRI images that imply a partial or complete failure of neurons to move correctly out of the proliferative and migration zones into the developing CP. Other types of heterotopia (PVH) point more towards problems at the apical ventricular lining. Over-migration phenotypes (including PMG) pinpoint instead problems of BM integrity, most likely causing progenitor detachment on the basal side. The relationships between type II lissencephaly and PMG are still not completely understood. However, consistently with previous hypotheses, these latter MCD seem not to involve problems of neuronal migration itself, but instead of the superficial cortical tissue environment that normally provides a template and barrier for migrating neurons.

One important step in moving toward a better understanding of MCD has been the identification of mosaic mutations and whole exome sequencing. Differences between the human and rodent brains are also beginning to be taken into account. For example, non-coding regions of DNA, including human accelerated regulatory enhancers (HAREs), also play important roles in human brain development by regulating developmental genes with different temporal and spatial dynamics compared to the mouse (Boyd et al., 2015).

As our knowledge of the genes and mechanisms involved increases, it has become clear that these disorders are quite heterogeneous. Patients with the same affected gene may show different brain malformations, and for many patients with MCD, the etiology remains unexplained. Despite this, patients with seemingly drastic differences in the extent and location of brain malformations nearly all show ID and epilepsy with the most commonly affected regions of the brain being the neocortex and hippocampus. This suggests that these brain areas may have unique developmental characteristics that increase susceptibility to malformations, and also that when these regions are malformed, neuronal circuits are prone to develop excitation/inhibition imbalances. On the other hand, the locations of malformations beyond the cortex may be related to the wider irreplaceable roles of certain genes in other brain regions during development. For example, *RELN* expression is required during migration in the cerebellum, and *TUBA1A/TUBB2B* during axonal outgrowth through the basal ganglia, explaining the co-occurrence of malformations in these regions in patients with these mutations.

Another point complicating human studies is that we may not see all neuronal migration disorders in patient MRIs. Delays in neuronal migration (but with ultimate normal positioning) can be deleterious for circuit formation and may contribute to psychiatric disorders, as discussed below. Studies of post-mortem brain tissue are informative, but the developmental origin of any findings cannot be confirmed, and causes and consequences cannot necessarily be distinguished.

Rodent models

One of the greatest accomplishments of rodent models used to study MCD genes is the large number of comparable studies in terms of molecular function (e.g., effect on neuronal migration *in vitro*, effects on MT dynamics, etc.). However, the link between molecular

function, physiology and behavior is still missing in most cases. Due to the variable techniques and experimental designs, in addition to the use of different mouse genetic backgrounds, it is hard to make direct comparisons from electrophysiology and behavioral studies, if indeed it has been possible to perform them (e.g., because of problems such as postnatal lethality). It would be extremely useful to see comparisons across models performed by the same group or in tight collaboration. Ventures for systematic phenotyping, such as the International Mouse Phenotyping Consortium, may help in this area in the future.

An observation commonly mentioned in neuronal migration literature is that mutations in genes that cause devastating effects during brain development in humans often have minor or spatially restricted effects in mouse models. Contrarily, mouse mutants that appear to be good models for human MCD sometimes involve genes that are not found to be mutated in patient populations (e.g., *p35* KO), perhaps because they are lethal. Unfortunately, the few mouse KO lines that recapitulate the severity of human MCD are often not viable (e.g., *Brdp* mouse), or do not have strong behavioral phenotypes (e.g., epilepsy in *reeler* mice). The increased structural complexity of the human brain, particularly the neocortex, is surely a major cause of mouse-human differences. One example contributing to this are the pallial SVZ progenitor subtypes that are rare in rodents. To overcome some of these problems, temporal and spatial control (e.g., RNAi, cKO models), or the use of gyrated brain animal models such as the ferret, are helping to compare roles of certain genes, e.g., (Borrell, 2010). In the future, the use of induced pluripotent stem cells, brain organoids grown *in vitro* (Lancaster et al., 2013) and “humanized” mouse models that increase primate-like progenitors and exhibit brain gyri, e.g., (Stahl et al., 2013), may further our understanding of some human MCD genes.

The use of *in utero* RNAi to reduce gene expression acutely during corticogenesis has revealed important insights not possible to identify in KO mice, and in the case of *Dcx* KD rats, has generated a relevant model for developmental epilepsy. However, in the vast majority of cases, RNAi studies are limited to embryonic or perinatal periods, and the effects of the gene in question during later stages of development are not investigated. For example, KD of *Tubb3* in mice causes a delay in neuronal migration (Saillour et al., 2014), which may lead to an anatomically subtle but relevant phenotype, as was the case for the fragile X mental retardation protein (Fmrp) (La Fata et al., 2014). In this case, KD of *Fmrp* (E14.5) caused a delay in the multipolar to bipolar transition via regulation of N-cadherin. There was no resulting layering deficit in the cortex, yet investigation of network dynamics and connectivity revealed an imbalance of excitation and inhibition (La Fata et al., 2014).

Indeed, correct timing of neural positioning in the CP, notably synchronization with INs arriving from the GE, has been hypothesized to prevent network imbalances that underlie psychiatric diseases such as ASD (Rubenstein and Merzenich, 2003). The spatial and temporal segregation of extracellular signals is exquisitely regulated during development (Draganova et al., 2015; Parthasarathy et al., 2014; Siegenthaler et al., 2009), and therefore delayed migration can be deleterious due to exposure to the wrong environment. A delay in migration may cause delays in maturation, which are hypothesized to underlie maladaptive compensatory mechanisms that ultimately lead to hyperexcitability, e.g., in *Dlx1* KO mice

and *Dcx* KD rats. Similarly, in rescue experiments with *Dcx* KD rats, neuronal migration deficits and the seizure phenotype were diminished with tamoxifen-induced *Dcx* reactivation at P0, but not at later dates (Manent et al., 2009). This rescue is therefore another example of a “delayed migration” model. It would be informative to determine whether IN maturation was normalized, or what other phenotypes persist at the behavioral, electrophysiological and synaptic levels. Perhaps delayed migration will constitute a subset of neuronal migration/neuropsychiatric animal models in the future.

Subtle changes in neuronal migration have also been suggested to predispose other psychiatric diseases. Genetic variants in *LIS1*, *RELN*, *VLDLR*, *NRG1* and its receptor *ERBB4* have all been associated with schizophrenic patients, and genes discovered in the context of schizophrenia have been found to play a role in neuronal migration, e.g., *DISC1*, which interacts with *LIS1* (Deutsch et al., 2010; Jaaro-Peled et al., 2009). Likewise, *ARX* and *DLX* have been associated with autism (Liu et al., 2009; Sherr, 2003). However, it is important to consider that several “neuronal migration genes” have roles postnatally that may be completely independent from migration, although still part of brain development and/or plasticity. Given the role of the cytoskeleton in synaptogenesis, it would not be surprising to find that mutations in many cytoskeletal-related proteins contribute to electrophysiological abnormalities observed in some animal models. Using a tamoxifen-induced cKO is a method to clearly demonstrate a role of a gene at different developmental and adult stages. For example, *p35* cKO mice that have normal neuronal positioning, unlike constitutive KOs, show decreased spine density in CA1 and L5 cortex in both postnatal and adults (Mita et al., 2014). As mentioned previously, reelin plays a role in synaptic function beyond perinatal stages, and recently it was shown that reelin expression in the vicinity of CA1 and L5 pyramidal cell distal dendrites is important for specifying the types of ion channels enriched in this cellular compartment (Kupferman et al., 2014).

RNAi studies are also largely limited to the dorsal neocortex at mid-corticogenesis or later (>E14.5 in mouse) given the relative technical ease to target this area. In order to understand the apparent vulnerability of the neocortex to mutations in genes regulating neuronal migration, it would be informative to compare RNAi targeting of a 3-layered cortex; for example, will knockdown of *Dcx* cause formation of an SBH in the piriform cortex? A closer inspection of the cortical area targeted may also reveal how mutations affect regions differently, e.g. *reeler* mouse high throughput *in situ* hybridization studies show that lamination patterns differ among several cortical areas (Boyle et al., 2011). The variable neuronal densities in different cortical areas in primates (Dehay and Kennedy, 2007), as well as the complexity of alternative splicing in different areas of human brain (Bae et al., 2014) can also deepen gene/phenotype comparisons in the future. Such complexities emphasize that rodent models can be limited when targeting regional problems.

Furthermore, the timing of RNAi certainly has implications for the resulting phenotype given the typical characteristics of neurons of different cortical layers. In the *Dcx* RNAi model, knockdown at E14 primarily targets L2–3 neurons. In *Dcx* KD rats, ectopic L2/3 neurons sent “normal” callosal projections to the contralateral cortex, but some also sent abnormal subcortical projections (Ackman et al., 2009). Given the propensity of L2/3 neurons to make cortico-cortical projections across brain hemispheres, their involvement

may be critical for synchronization of large networks of neurons via creation of a reciprocal excitation.

Knockdown at earlier time points in order to target L5–6 neurons would be interesting for several reasons. The composition of rodent heterotopia may be different in terms of layer specific markers, leading to perhaps a greater increase in subcortical projections from the heterotopia and different electrophysiological effects. The *Mekk4* KO mouse would be a potential model to examine, given the early-born composition of the PVH in this model (Sarkisian et al., 2006), but these mice appear not to survive after birth. On the other hand, given the physical barrier that would result as a consequence of stalled early-born neurons, late-born neurons might become delayed as well. However, as revealed recently in *HeCo* mice, early-born neurons do become delayed in the developing heterotopia, but somehow manage to migrate to their proper positions whereas late-born cells, perhaps for timing and positional reasons, remain trapped. Therefore, it seems more probable that a heterotopia would contain late-born neurons, and indeed in brains from humans with PVH and SBH, this has been shown to be the case. Callosal problems are variable, if they exist at all, and it is not known whether projection patterns from heterotopic neurons are similar to those seen in animal models. Diffusion tensor imaging studies may shed further light on white matter abnormalities in the future.

SBH

As mentioned above, in adult *HeCo* mice, early-born neurons are correctly situated, making it appear as if they were never delayed at all during development. Most other rodent models contain some early-born neurons in the SBH, although the majority are always late-born. In these cases the hypothesis of early-born neurons forming a barrier for late-born neurons seems less likely. In the *Rapgef2* cKO, neurons of different birthdates are randomly positioned, whereas the SBH in the *Tish* rat and *RhoA* cKO are organized concentrically with late-born neurons around the rim of the heterotopia. It is difficult to speculate how these different organizations result, but this is an interesting area for future studies.

One surprising finding with several SBH rodent models is that the cause of the neuronal migration defects appears to be secondary to progenitor defects (*HeCo*, *Tish*, *RhoA* cKO). Progenitor effects should be investigated in the other models, although acute RNAi targeting of *Dcx* and *Rapgef2* seemed instead to affect post-mitotic cells outside of the proliferative zones. It is obviously unclear whether this is exactly the situation in human brains, but nevertheless, it seems to suggest that multiple mechanisms might give rise to SBH.

Another surprising finding from SBH rodent models is that the normotopic cortex, not heterotopic, is likely the site of epileptogenesis. However, it is less surprising when compared to other focal models of neurodevelopmental origin that indicate excitation/inhibition imbalances only in the vicinity of the brain malformation. Humans with tuberous sclerosis complex (TSC) have benign brain tumors composed of dysplastic heterotopic neurons with aberrant dendrites and axons, and like patients with MCD, this disease is associated with ID and early onset epilepsy (Holmes and Stafstrom, 2007). Modeling TSC in mice is difficult (Bozzi et al., 2012), but studies in human brain tissue demonstrate hyperexcitability and changes in glutamate/GABA receptors in cortical tissue surrounding

tubers (Major et al., 2009). Freeze-lesion induced neocortical dysplasias, used to mimic human PMG, also cause hyperexcitability in cortical areas adjacent to the induced microgyrus, with spreading to the hippocampus e.g., (Peters et al., 2004; Takase et al., 2008). The mechanisms that underlie this phenomenon are currently unknown, but this might imply that deficiency within surrounding or overlying cortical areas is more epileptogenic than the aberrant ectopic tissue itself (e.g., the SBH in the white matter).

Models for developmental epilepsy

There are only a few neuronal migration disorder animal models that exhibit spontaneous epilepsy, and in several cases the onset has not yet been explored. This could be an important characterization of these models given that the onset of seizures in humans with *LIS1* and *DCX* mutations correlates with the severity of the malformation; the most severe cases are obvious within the first few days after birth, whereas ‘less severe’ malformations are associated with epilepsy appearing during adolescence (e.g. for females with *DCX* mutations (Bahi-Buisson et al., 2013). The developmental onset of seizures in mice is more difficult to monitor physiologically (inability to permanently implant indwelling electrodes in young animals), but further indirect studies correlating the onset of epileptic activity (e.g., using histological markers) may provide greater insight into the development of epilepsy, and potential therapeutic interventions.

The immature brain is more prone to seizures than the adult brain (Ben-Ari and Holmes, 2006), but often studies in mice suggest that seizures do not occur until after weaning. The earliest report of seizures in a model of neuronal migration disorders is at P21, e.g., in *Dcx(-/Y)/Dcl2(-/-)* mice (Kerjan et al., 2009). On the other hand *Dcx* KO and *p35* KO mice with spontaneous seizures were only reported at 3 months old (Nosten-Bertrand et al., 2008; Wenzel et al., 2001) or 36–49 days old, respectively (Greenwood et al., 2009). In both cases earlier onset cannot however be disregarded as it was not investigated. In *Dcx* KD rats, there was no evidence of spontaneous seizures in juveniles (Lapray et al., 2010). Earlier seizures (starting at P14), have been observed (without physiological recording) in models that do not display neuronal migration abnormalities, for example in *Kif5a* cKO mice (Nakajima et al., 2012), in models of TSC (Zeng et al., 2011), and in *Lgi1* KO mice (Fukata et al., 2010). Notably, in these cases seizures were frequent and severe, probably leading to early death. The relative infrequency of seizures in *Dcx* KO and *Lis1* (+/-) mice, and in *p35* KOs that live until adulthood, may be the reason they have not been observed at younger ages, although this may also be related to the nature of the seizure, their activity-dependence, and potentially the genetic backgrounds. Yet, it still remains possible that the mouse brain is less susceptible to seizures than the human brain.

CA3 may be a particularly vulnerable site in rodents for both neuronal migration defects and initiation of seizure activity, as discussed previously (Belvindrah et al., 2014). A large increase in CA3 recurrent axon collaterals occurs during postnatal weeks 2 and 3, and is normally followed by a 50% elimination (Gomez-Di Cesare et al., 1997); a deficit in pruning could provide the morphological means for recurrent excitation in the adult circuit. Perhaps supporting this hypothesis, blockade of neuronal activity, which is required for pruning, in CA3 with tetrodotoxin during this 2 week time period resulted in chronic epilepsy in

adulthood (Galvan et al., 2000). Concerning *Dcx* KO mice, the question remains if spontaneous seizures are initiated in CA3. CA1 neurons are also hyperexcitable; however, it is unknown if this is autonomous or a downstream effect of CA3 hyperexcitability. In general, it may be useful to make KO mice specific to DG, CA1 or CA3 in epilepsy mouse models with hippocampal lamination defects to understand the contribution of each region to circuit abnormalities and epileptogenic activity.

New information about birthdate-dependent circuit organization could provide new testable hypotheses for dysfunction in MCD models. In mouse models with lamination abnormalities, it is unknown whether clonally-related neurons are interconnected in the same stereotypical way as in unmodified mice. There may be direct or indirect roles for neuronal migration genes in the formation of these circuits, for example if association with RG processes or correct arrival time in the CP are required. Numerous other possibilities exist, including changes in the number of sister neurons produced from a single progenitor, or the radial alignment of pallial-derived sister neurons into a functional cortical column. It would be particularly interesting to investigate distribution of clonally related neurons in SBH or over-migration phenotypes to see whether sister neurons preferentially under or over-migrate together, or do not but maintain stereotypical interconnectedness.

Finally, it is important to consider diet regimens when interpreting behavioral data. Many behavioral tests with rodents routinely use calorie restriction to increase motivation; studies on acute and chronic calorie restriction have revealed changes in synaptic plasticity that likely underlie robust behavioral changes, including enhanced learning and memory performance (Murphy et al., 2014). The benefits of either calorie restriction or ketogenic diets have also long been known to reduce seizures (Ruskin and Masino, 2012; Yuen and Sander, 2014). The reduction in blood glucose and shift to ketone bodies as a source of energy appear to be important physiological changes induced by these diets, although the mechanisms underlying this anticonvulsive/neuroprotective effect remain elusive. Evidence in rodent models again indicates changes in synaptic plasticity, and also the increased availability of high-energy molecules and mitochondria. Deficits in energy metabolism is a relatively unexplored topic in MCD animal models, although abnormal mitochondria were observed in *Dcx* KO mice (Khalaf-Nazzal et al., 2013). The effects of calorie restriction may have different effects on seizure prone mice, which may also depend on diet duration (Ruskin and Masino, 2012). Therefore, calorie restriction used in learning/memory tests may enhance cognition in mutants, concealing an initial deficit.

Conclusion

We have discussed here many aspects (molecular, cellular, physiological and functional) related to neuronal migration and associated disorders. There have been numerous advances on the molecular front, and next generation sequencing of patient DNAs will continue to reveal molecules important for brain development. At the cellular level, as we have explored, 'neuronal migration defects' can arise both intrinsically, as well as by perturbation of the cortical environment (apical or basal membranes, RG cells, etc.). With abnormal neuronal position, epileptogenesis is often observed, not necessarily in close proximity to the anatomically obvious lesion. Neuronal connectivity needs to be carefully studied to further

understand these problems, and ultimately, the cognitive deficits and epilepsy phenotype of humans with MCD and the associated rodent models point to a circuitry problem. Careful and systematic behavioral experiments in relevant models on similar genetic backgrounds may shed further light on the consequences of these disorders.

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Abbreviations

A	astrocyte
AP	anterior-posterior
ASD	autism spectrum disorder
BP	basal progenitors
CA	cornu ammonis
CC	corpus callosum
CGE	caudal ganglionic eminence
cKO	conditional knockout
CP	cortical plate
CR	Cajal-Retzius
DG	dentate gyrus
DV	dorsal-ventral
E	embryonic day (e.g., E12)
EEG	electroencephalogram
EPM	elevated plus maze
GABA	gamma-amino butyric acid
GEF	guanine nucleotide exchange factor
GW	gestational week
H	hippocampus
HAREs	human accelerated regulatory enhancers

ID	intellectual disability
INs	interneurons
IPs	intermediate progenitors
IPSC	inhibitory post-synaptic current
IZ	intermediate zone
KD	knockdown (via RNAi)
KO	knockout
LV	lateral ventricle
MAPs	microtubule associated proteins
MCD	malformations of cortical development
MCPH	primary microcephaly (literally “microcephaly primary hereditary”)
mEPSC	miniature excitatory post-synaptic current
MGE	medial ganglionic eminence
MRI	magnetic resonance imaging
MT	microtubules
MWM	Morris water maze
MZ	marginal zone
NCx	neocortex
OB	olfactory bulb
OPCs	oligodendrocyte precursor cells
oRGs/bRGs	outer/basal radial glial-like
OSVZ	outer SVZ
PMG	polymicrogyria
PN	projection neuron
PPF	paired pulse facilitation
PVH	periventricular heterotopia
RG	radial glial
RNAi	RNA interference
SBH	subcortical band heterotopia

sEPSC	spontaneous excitatory post-synaptic current
SNPs	short neural precursors
SVZ	subventricular zone
TSC	tuberous sclerosis complex
VZ	ventricular zone

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Figure 1. Rodent neocortical development

a. Schematic representation of the developing rodent neocortex. Glutamatergic PNs produced in the dorsal telencephalon (pallium) migrate radially to generate the neocortex and hippocampus. Cortical inhibitory INs generated in the ventral telencephalon (subpallium) migrate tangentially. **b.** Early in development (E12), RG cells located in the VZ divide symmetrically (curved black arrow) to generate two more RGs, or asymmetrically to produce neurogenic progenitors (IPs/SNPs) or neurons that migrate via somal translocation toward the MZ. **c-d.** Later in development (E14–18), IPs located in the SVZ are the primary source of neurogenic divisions. SNPs remain in the VZ, and are possibly precursors for IPs. At this stage, neurons first migrate via RG cell guided locomotion followed by somal translocation. INs arriving from the subpallium migrate tangentially to the cortex, then radially to reach their final destinations. RG cells also give rise to OPCs, which produce oligodendrocytes, and astrocytes. Some RG processes in the hippocampus bend (**c**), causing clonally related neurons to be distributed horizontally. Clonally related neurons in the neocortex (**d**) form radial functional columns with layer specific input and output connectivities.

Abbreviations: NCx= neocortex; LV= lateral ventricle; H= hippocampus; LGE= lateral geniculate nucleus; MGE=medial geniculate nucleus; Str= striatum; MZ= marginal zone; CP= cortical plate; SVZ= subventricular zone; IZ= intermediate zone; VZ= ventricular zone; RG= radial glial cell; SNP= short neural precursor; IP= intermediate progenitor; PN= projection neuron; IN= interneuron; OPC= oligodendrocyte precursor cell; A= astrocyte; CR= Cajal-Retzius cell

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Figure 2. MCD genes and cytoskeletal regulatory pathways

Schematic representation of proteins regulating MTs and actin in a migrating post-mitotic neuron. In general, MT regulating proteins are shown in green, and actin regulating proteins are shown in orange. Disruption of cytoskeletal proteins and their regulatory pathways leads to various consequences. Mutations in MAPs (Dcx, Dclk, Tau, Map2, Map1b), which stabilize MTs, can impair polarization, formation of the leading process, neurite outgrowth and/or lead to excessive branching that hinders migration. Lis1/Ndel1/dynein are required for nuclear movement during migration. Molecular motors, such as dynein and kinesins, serve important roles in migration by transporting cargo in opposite directions along MTs, or by transporting MTs themselves. Mutations in components of the reelin pathway lead to impaired migration, interactions with RG cells and final positioning of neurons via impaired regulation of cytoskeletal dynamics. Actin plays complex roles in the growth cone and trailing processes of migrating neurons, with mutations in regulatory pathways leading to overmigration or migration arrest, which may be consequential to progenitor defects observed in various rodent models.

Figure 3. Schematic diagrams of selected MCD rodent model neocortical and hippocampal phenotypes.

Schematic representations of morphological characteristics shown on coronal hemi-sections for adult animals. Hippocampal subregions are indicated in control. Location of early-born (purple, E12–13) and late-born (blue, E14–16) pyramidal neurons are depicted by dots in neocortex and SBH, and layer 1 by a grey line. INs are not displayed. In general, early-born and late-born neurons are considered to be L5–6 and L2–4, respectively, except in the case of the *reeler* mouse, which may show more complicated layer distributions in certain subregions (see Boyle et al., 2011). Discrete lamination defects or general dispersion of pyramidal cells or DG granule cells in the hippocampus are represented by multiple or thick lines, respectively. Changes in the corpus callosum (CC) are indicated by changes in line thickness or dispersion of line into SBH (*Rapgef2* cKO, *p35* KO). An abnormal layer 1 is depicted in the *reeler* mouse. Wavy L2–4 are depicted in *Tuba1a* mouse.

Abbreviations: DG = dentate gyrus, LV = lateral ventricle, CC = corpus callosum

Table 1.

Human MCD genes and phenotypes

Gene	MCD type	Major pathways/ roles	Clinical symptoms	Syndromes	References
TYPE I LISSENCEPHALY					
<i>DCX</i>	males: lissencephaly	MT stability; neuronal migration	ID, epilepsy		Des Portes et al., 1998b; Gleson et al., 1998; Sicca et al., 2003; Guerrini and Marini, 2006; Bahi-Buisson et al., 2013;
	females: subcortical band heterotopia (SBH)		ID, epilepsy		
<i>LIS1 (PAFAH1B1)</i>	lissencephaly /SBH	MT binding; dynein binding ; neuronal migration; nucleokinesis ; progenitors	ID, epilepsy		Des Portes et al., 1998b; Reiner et al., 1993
<i>14-3-3ϵ (YWHAE)</i>	lissencephaly with craniofacial abnormalities	intracellular signaling; MT	ID, epilepsy	Miller-Dieker	Reiner et al., 1993
<i>KIF2A</i>	heterotopia, agyria, pachygyria, SBH, thin CC, congenital microcephaly	kinesin; MT-associated motor	ID, epilepsy ; dev delay		Poirier et al., 2013
<i>ARX</i>	lissencephaly; CC agenesis	transcription factor ; tangential migration INs	ID, epilepsy	X-linked lissencephaly with abnormal genitalia (XL-AG)	Kitanura et al., 2002; Kato et al., 2004
<i>EML1</i>	ribbon like SBH; PMG	MT binding protein; mitotic spindle; progenitors	ID, epilepsy		Kielar et al., 2014
<i>TUBA1A</i>	lissencephaly/SBH; cerebellar hypoplasia possible ; congenital microcephaly	MT component	ID, epilepsy, motor delay ; tetraplegia	Can involve other brain structures	Keays et al., 2007; Poirier et al., 2007; Bahi-Buisson et al., 2010
<i>TUBG1</i>	Laminar heterotopia, agyria, pachygyria, microcephaly ; dysmorphic CC	MT component ; radial migration	ID, epilepsy		Poirier et al., 2013
<i>ACTG1</i>	lissencephaly	actin component	ID, epilepsy, progressive hearing loss	Baraitser-Winter syndrome	Verloes et al., 2015
<i>ACTB</i>	lissencephaly	actin component	ID, epilepsy, dystonia	Baraitser-Winter syndrome	Verloes et al., 2015
<i>NDE1</i>	micro-lissencephaly	nuclear migration; centrosome duplication; mitotic spindle assembly	ID, epilepsy		Alkuraya et al., 2011
<i>VLDLR</i>	lissencephaly with cerebellar hypoplasia	reelin receptor ; neuronal migration and placement	ID, epilepsy, cerebellar ataxia	Disequilibrium syndrome	Schlotawa et al., 2013
<i>RELN</i>	lissencephaly with cerebellar hypoplasia	secreted extracellular matrix protein; neuronal migration and placement	ID, epilepsy		Hong et al., 2000
<i>FLNA</i>	periventricular heterotopia (PVH)	actin binding protein; actin crosslinking	ID, epilepsy; broad range of congenital malformations	Otopalatodigital syndromes Melnick-Needles syndrome Cardiac valvular dysplasia	Fox et al., 1998; Sheen et al., 2004; Parrini et al., 2006

Gene	MCD type	Major pathways/ roles	Clinical symptoms	Syndromes	References
<i>ARHGEF2</i>	PVH with microcephaly	trafficking; cell-cell adhesion; radial migration; Rac/Rho signaling; interacts with FLNA	ID, epilepsy		Sheen et al., 2004; Sheen et al., 2014
<i>C6orf70</i>	PVH	trafficking; cell-cell adhesion	ID, epilepsy, facial dysmorphism		Conti et al., 2013
<i>FAT4</i>	PVH	protocadherin; cell-cell adhesion; apical membrane	ID, epilepsy, skeletal dysplasia, facial dysmorphism	Van Maldergem Syndrome 2; Hennekam Lymphangiectasia-Lymphedema Syndrome 2	Cappello et al., 2013
<i>DCHS1</i>	PVH	protocadherin; FAT4 ligand; cell-cell adhesion; apical membrane	ID, epilepsy, skeletal dysplasia, deafness	Van Maldergem Syndrome 1	Cappello et al., 2013
Gene	MCD type	Major pathways	Clinical symptoms	Syndromes	References
TYPE2 LISSENCEPHALY/POLYMICROGYRIA (PMG)					
<i>POMT1, POMT2</i>	cobblestone cortical malformation	O-glycosylase; integrity of pial-glial limitans; neuronal migration stop signal	ID, muscular dystrophy	muscle-eye-brain disease (MEB)	Mercuri et al., 2009
<i>FKRP</i>	cobblestone cortical malformation	O-glycosylase; integrity of pial-glial limitans	+/- ID; muscular dystrophy	MEB or Walker-Warberg syndrome (WWS)	Mercuri et al., 2009
<i>FCMD</i>	cobblestone cortical malformation	O-glycosylase; integrity of pial-glial limitans	+/- ID; muscular dystrophy	WWS; Fukuyama congenital muscular dystrophy	Mercuri et al., 2009
<i>LARGE, POMGNT1</i>	cobblestone cortical malformation	O-glycosylase; integrity of pial-glial limitans	+/- ID; muscular dystrophy	MEB	Mercuri et al., 2009
<i>GPR56</i>	Bilateral fronto-parietal PMG and/or cobblestone malformation; white matter abnormalities; cerebellar dysplasia	G-protein coupled receptor; integrity of basal lamina and pial-glial limitans	ID, epilepsy, cerebellar ataxia		Bahi-Buisson et al., 2010
<i>TUBB2B</i>	PMG	microtubule component ; radial migration	ID, epilepsy		Jaglin et al., 2009
<i>SRPX2</i>	PMG	secreted proteoglycan	ID, epilepsy, speech dyspraxia		Royer-Zemmour et al., 2008; Roll et al., 2010
<i>PAX6</i>	PMG	transcription factor ; progenitors ; arealization of cortex	ID, cerebellar ataxia, various eye abnormalities	Atypical Gillespie Syndrome and others	Glaser et al., 1994
<i>TBR2</i>	PMG	transcription factor; progenitors	Early lethality	Microcephaly	Baala et al., 2007
MICROCEPHALY					
<i>ASPM</i>	primary microcephaly (MCPH); abnormal gyri	mitotic spindle protein; cell cycle; symmetric progenitor division	ID, speech delay, seizures variable, short stature		Fish et al., 2006
<i>MCPH1</i>	MCPH	mitotic spindle protein; cell cycle; chromosome condensation	ID, seizures variable, short stature		Gruber et al., 2011
<i>STIL</i>	MCPH	centriole amplification; cell cycle	ID, seizures variable, short stature		Arquint and Nigg, 2014

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Gene	MCD type	Major pathways/ roles	Clinical symptoms	Syndromes	References
<i>CDK5RAP2</i>	MCPH	centrosome/spindle integrity; cell cycle	ID		Lizarraga et al, 2010
<i>CENPI</i>	MCPH	centrosome/spindle integrity; cell cycle	ID, seizures variable		Insolera et al., 2014
<i>WDR62</i>	microcephaly with simplified gyral pattern (MSGP)	centrosome/spindle integrity; cell cycle	ID, delayed psychomotor dev, seizures variable		Yu et al., 2010
<i>KIF5C</i>	MSGP	centrosome/spindle integrity; cell cycle	ID, seizures		Poirier et al., 2013

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Table 2.

Cortical developmental timeline: human versus mouse

	Mouse	Human
<i>Onset neurogenesis</i>	E10–11	GW5–6
<i>SVZ formed</i>	E12	GW5–6
<i>Appearance of cortical plate</i>	E14	GW7–8
<i>OSVZ formed</i>		GW11
<i>Neuronal migration peak</i>	E13–16	GW12–20
<i>6 layered cortex formed</i>		GW28
<i>Birth</i>	E20–21	GW40

Abbreviations: SVZ= subventricular zone; OSVZ= outer SVZ; E= embryonic day; GW= gestational week

Table 3a.
Rodent models related to lamination defects in rodents and humans: Morphological phenotypes

	Protein exp.	Cortical lamin. defect	Hippo. Lamin. defect	CB lamin. defect	Other	White matter defects	Abnormal dendrites/ axons (<i>in vivo</i>)	Enlarg. Vent.	Refs
Tubala (Jna1^{-/-}) mouse	neurons	minor L2-4	CA1, CA3	-	superior colliculus	-	-	-	Keays 2007; Edwards 2011
Tubb2b KO mouse	Progen.; neurons	minor	-	-	Inc apoptosis	+	-	+	Stottman 2013
Lis1 (+/-) mouse	Progen.; neurons	-	CA1, CA3, DG	-	-	-	Dec basal den CA1; Inc basal den DG	-	Hirotsune 1998; Fleck 2000; Greenwood 2009; Jones & Baraban 2007; Paylor 1999
Dcx (-/Y) mouse	neurons	-	CA3	-	-	SV/Pas only	Dec den CA3; Inc mossy fibers CA3	-	Corbo 2002; Kappeler 2007; Nosten-Bertrand 2008; Bazzelot 2012; Germain 2013
Dcx/Dcl1 KO mouse	Progen.; neurons	+	CA1, CA3, DG	+	thalamus brainstem	+	-	+	Deuel 2006
Dcx/Dcl2 KO mouse	Progen.; neurons	-	CA1, CA3	-	-	-	Dec den CA1; mossy fibers	-	Kerjan 2009
Map2/Map1b KO mouse	neurons	+	+	+	OB; inf olive; pons	+	-	-	Teng 2001
Tau/Map1b KO mouse	neurons	-	+	-	-	+	-	-	Takei 2000
Kif2a KO mouse	neurons	+	CA1, CA3	+	Brainstem; CB nuclei	+	Inc axon collaterals CA1 & cortex	-	Homma 2003
Cdk5 KO mouse	neurons	+, inverted	+	+	brainstem	-	-	-	Ohshima 1996
Cdk5 cKO mouse (CamKII-Cre)	neurons	+, inverted	+	-	progressive neurodegen; gliosis	-	-	-	Takahashi 2010
p35 KO mouse	neurons	+, inverted	+	+	OB	+	cortex both; DG both	-	Chae 1997 ; Wenzel 2001 ; Patel 2004
Reeler mouse	CR cells (reelin)	+, inverted	CA1, CA3, DG	+	Brainstem; CB nuclei	-	Diffuse mossy fibers; dec spines CA1	-	Boyle 2011; Parlylo 2006; Parlylo & Willingham 2006; Kopias 2006; D'Arcangelo & Curran 1998; Hellwig 2011; Liu 2001

“Abnormal cellular (axons/dendrites)” does not include INs. IPSCs/EPSCs refer to recordings from pyramidal neurons. For physiology, “+” indicates increased excitability.

Table 3b. Rodent models related to lamination defects in rodents and humans: Physiological and behavioral phenotypes

	Physiology (in vitro)		Behavior				Genetic background	Refs
	Abnormal inhibitory	Abnormal excitatory	Spont. epilepsy	Inc. susceptibility	Learning/Memory deficits	Other deficits		
Tubala (Jna^{-/-}) mouse	–	–	?	–	Working memory (T-maze)	Dec anxiety (EPM); hyperactive; inc. acoustic startle	F1 : BALB/cAnN x C3H/HeH; or C3H	Keays 2007; Edwards 2011
Tubb2b KO mouse	–	–	–	–	–	Perinatal lethal	Mixed A/J x FVB	Stottman 2013
Lis1 (+/-) mouse	Inc IPSP/IPSC CA1; +INs	Inc EPSP; PPF CA1; +CA1	+ (>P36)	–	Spatial memory (MWM)	Rotorod	Mixed 129SvEv x NIH Black Swiss	Hirotsune 1998; Fleck 2000; Greenwood 2009; Jones & Baraban 2007; Paylor 1999
Dcx (-/Y) mouse	Inc IPSC CA1/CA3	+CA1 +CA3	+ (>3 mo)	+	Normal	Abnormal social; lateralization	C57BL/6N for behavior	Corbo 2002; Kappeler 2007; Nosten-Bertrand 2008; Bazet 2012; Germain 2013
Dcx /Dcl1 KO mouse	–	–	–	–	–	Perinatal lethal	Mixed 129/ SvJ x C57BL/6J	Deuel 2006
Dcx/Dcl2 KO mouse	Dec IPSC CA1	–	+ (>P21)	–	–	Dec survival rate post P21	Mixed Sv/129 x C57BL/6N	Kerjan 2009
Map2/Map1b KO mouse	–	–	–	–	–	Perinatal lethal	Mixed 129SV/ C57BL/6J	Teng 2001
Tau/Map1b KO mouse	–	–	–	–	–	Perinatal lethal	Mixed 129SV/ C57BL/6J	Takei 2000
Klf2a KO mouse	–	–	–	–	–	Perinatal lethal	C57BL/6J	Homma 2003
Cdk5 KO mouse	–	–	–	–	–	Pre/Perinatal lethal	C57BL/6	Ohshima 1996
Cdk5 cKO mouse (CamKII-Cre)	–	–	+ (>2 mo)	–	–	Dyskinesia; dec survival rate >P21	C57BL/6	Takahashi 2010
p35 KO mouse	–	–	+ (>3 mo)	+ (>2 mo)	–	Dec survival rate >P21	Mixed C57BL/6 x 129/Sv	Chae 1997; Wenzel 2001; Patel 2004

	Physiology (in vitro)		Behavior				Genetic background	Refs
	Abnormal inhibitory	Abnormal excitatory	Spont. epilepsy	Inc. suscep convuls	Learning/Memory deficits	Other deficits		
Reeler mouse	Dec PPF CA1	-	-	+ (> 3 mo)	Confounded by motor deficits	Ataxia, other motor	BoC3Fe (<i>r</i> ^{4d})	Boyle 2011; Patrylo 2006; Patrylo & Willingham 2006; Kopjas 2006; D’Arcangelo & Curran 1998; Hellwig 2011; Liu 2001

“Abnormal cellular (axons/dendrites)” does not include INs. IPSCs/EPSCs refer to recordings from pyramidal neurons. For physiology, “+,” indicates increased excitability.

Abbreviations: DG = dentate gyrus, IPSC = inhibitory postsynaptic current, EPSC = excitatory postsynaptic current, OB = olfactory bulb, PPF =paired pulse facilitation, MWM = Morris water maze, EPM = elevated plus maze

Table 4a. Subcortical band heterotopia and periventricular heterotopia rodent models: Morphological phenotypes

	Protein exp.	Other Lamination defects	SBH/PVH	Ectopic progenitors	White Matter defects	Abnormal dendrites/axons	Enlarged ventricles/other	Refs
Dcx KD rat (E15–16)	neurons	–	SBH	–	–	SBH den/axons	–	Bai 2003; Lapray 2010; Petit 2014
Lis1 KD rat (E16)	Progen.; neurons	–	SBH	–	–	–	–	Tsai 2005
Tish rat	Unknown gene	–	SBH	+	–	SBH den/axons	+	Lee 1997; Lee 1998 ; Schottler 1998; Chen 2000; Trotter 2006; Fitzgerald 2011
HeCo mouse	Progen.; neurons	–	SBH	+	–	–	+	Kielar 2014; Croquelois 2009
RhoA cKO mouse (Emx1-Cre)	Progen.; neurons	–	SBH/subpial ectopia	+	–	–	–	Cappello 2012
Rapgef2 cKO mouse (Emx1-Cre)	neurons	CA1	SBH	–	+	SBH	+	Bilasy 2009
Fina KD rat (E15)	Progen.; neurons	–	PVH	–	–	–	–	Carabalona 2012
Mekk4 KO mouse	Progen.; neurons	Subpial ectopias, PMG	PVH	–	–	–	Exencephaly; inc apoptosis	Sarkisian 2006
Big2 KO mouse	Progen.; neurons	Subependymal heterotopia	PVH	+	–	–	exencephaly	Zhang 2012

In models with SBH, “cortical lamination defect” refers to normotopic cortex only. “Abnormal cellular (axons/dendrites)” does not include INs. IPSCs/EPSCs refer to recordings from pyramidal neurons. For physiology, “+” indicates increased excitability. Spontaneous epilepsy indicates confirmation with EEG recording.

Table 4b. Subcortical band heterotopia and periventricular heterotopia rodent models: Physiological and behavioral phenotypes

	Physiology (in vitro)		Behavior				Genetic background	Refs
	Abnormal inhibitory	Abnormal excitatory	Spontaneous epilepsy	Inc suscep. convulsants	Learning/Memory deficits	Other		
Dcx KD rat (E15–16)	Delayed maturation heterotopic	Inc EPSC normotopic; Delayed maturation heterotopic	+	+	–	hyperactive	Wister	Bai 2003; Lapray 2010; Petit 2014
Lis1 KD rat (E16)	–	–	–	–	–	–	Sprague–Dawley	Tsai 2005
HeCo mouse	–	–	?	+ (>3 mo)	MWM	hypokinesia	NOR/CDI	Kielar 2014; Croqueolois 2009
Tish rat	Dec IPSC normo & heterotopic	–	+(adult)	–	–	–	Sprague–Dawley	Lee 1997; Lee 1998; Schottler 1998; Chen 2000; Trotter 2006; Fitzgerald 2011
RhoA cKO mouse (Emx1–Cre)	–	–	–	–	–	–	N/A	Cappello 2012
Rapgef2 cKO mouse (Emx1–Cre)	–	–	?	+ (>2 mo)	–	–	Mixed C57BL/6 × ICR	Bilasy 2009
Fina KD rat (E15)	–	–	?	+ (P30)	–	–	Wister	Carabona 2012
Mekk4 KO mouse	–	–	–	–	–	Perinatal lethal	C57BL/6	Sarkisian 2006
Big2 KO mouse	–	–	–	–	–	Perinatal lethal	C57BL/6	Zhang 2012

In models with SBH, “cortical lamination defect” refers to normotopic cortex only. “Abnormal cellular (axons/dendrites)” does not include INs. IPSCs/EPSCs refer to recordings from pyramidal neurons. For physiology, “+” indicates increased excitability. Spontaneous epilepsy indicates confirmation with EEG recording.

Abbreviations: SBH = subcortical band heterotopia, PVH = periventricular heterotopia, DG = dentate gyrus, IPSC = inhibitory postsynaptic current, EPSC = excitatory postsynaptic current, PPF = paired pulse facilitation, MWM = Morris water maze, EPM = elevated plus maze