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Review

# The right neuron at the wrong place: biology of heterotopic neurons in cortical neuronal migration disorders, with special reference to associated pathologies

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**Abstract.** During the development of the neocortex, neurogenesis and neuronal differentiation occur in two separate locations. Thus neurons have to migrate through the future white matter. Arrested or excessive migration leads neurons to differentiate in a heterotopic position. Such neuronal migration disorders (NMDs) occur sporadically in normal development but are markedly increased as a consequence of genetic defects or after exposure to toxic drugs during the period of migration. Anatomofunctional studies in rodents with NMDs have revealed that heterotopic neurons form essentially normal afferent and efferent connections, which has been interpreted as evidence that the connection pattern of cortical neurons is specified prior to migration. In addition, recent data show that heterotopic neurons can be contacted by environmental, that is local, fibres that normally never innervate the neocortex. This dual connectivity leads heterotopias to form bridges between their environmental and original network. Such an abnormal pattern of connectivity could contribute to the pathophysiology of disorders associated with NMDs such as epilepsy.

**Key words.** Neurogenenin; neocortex; development; epilepsy; schizophrenia; dysplasia.

## Introduction

The neocortex is a thin layer of grey matter that forms the external part of the cerebral hemispheres. Histologically, the mammalian neocortex is formed by six layers that can be distinguished by the size, shape and pattern of connections of their constituent neurons. Most neocortical neurons originate from the proliferative neuroepithelium that forms the external border of the neural tube. After completing their last mitosis, neurons engage into a long migration through the intermediate zone (future white matter) toward the cortical plate where they settle and differentiate (normal cortical development is summarised in fig. 1). Neuronal migration in the neocortex occurs between the 8th and the 20th weeks of gestation [1] in humans, and between E14 and P5 in rats [2].

The process of neuronal migration involves three main steps: (i) commitment to a specific cortical layer, (ii) migration proper and (iii) cessation of migration in the appropriate layer. These three steps are under different control mechanisms. Briefly, neuroblasts become determined to develop into a laminar subtype during the S phase of their final division by presently unidentified molecular cues, as evidenced by the results of heterochronic transplantation [3–7]. The migration proper is guided by the processes of radial glial cells that span radially from the ventricular zone to the pial surface

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[8–11]. Neuronal locomotion is achieved by a complex neuronal machinery [12] that can be modulated by cell-cell and cell-matrix interactions [13–15] as well as by ionic flux [16, 17]. Finally, the end of the migration involves the detachment from the radial glia fibres triggered by local signals [18–20], some of them emitted by the Cajal-Retzius cells of the marginal zone (reviewed in [21, 22]).

This very brief presentation of cortical migration hints at the complexity of the processes involved in this phenomenon. Thus it is not surprising that migration can be perturbed by mutations, teratogenic (e.g. alcohol or cocaine), physical (e.g. irradiation) and biological (e.g. viral infection) influences that occur during the period of migration. The use of such agents has therefore provided animal, primarily rodent, models of neuronal migration disorders (NMDs). The paradigmatic genetic model is the *reeler* mutant mouse ([23], fig. 1), which belongs to the expanding family of transgenic mice with a *reeler*-like phenotype [24–26]. Nongenetic models have been generated by exposure of pregnant females during the early period of migration to irradiation or toxic substances such as the antimitotic agent methylazoxymethanol (MAM) [27, 28], cocaine [29] or ethanol [30, 31]. Whatever their respective mechanisms, all these influences will lead neurons to differentiate in

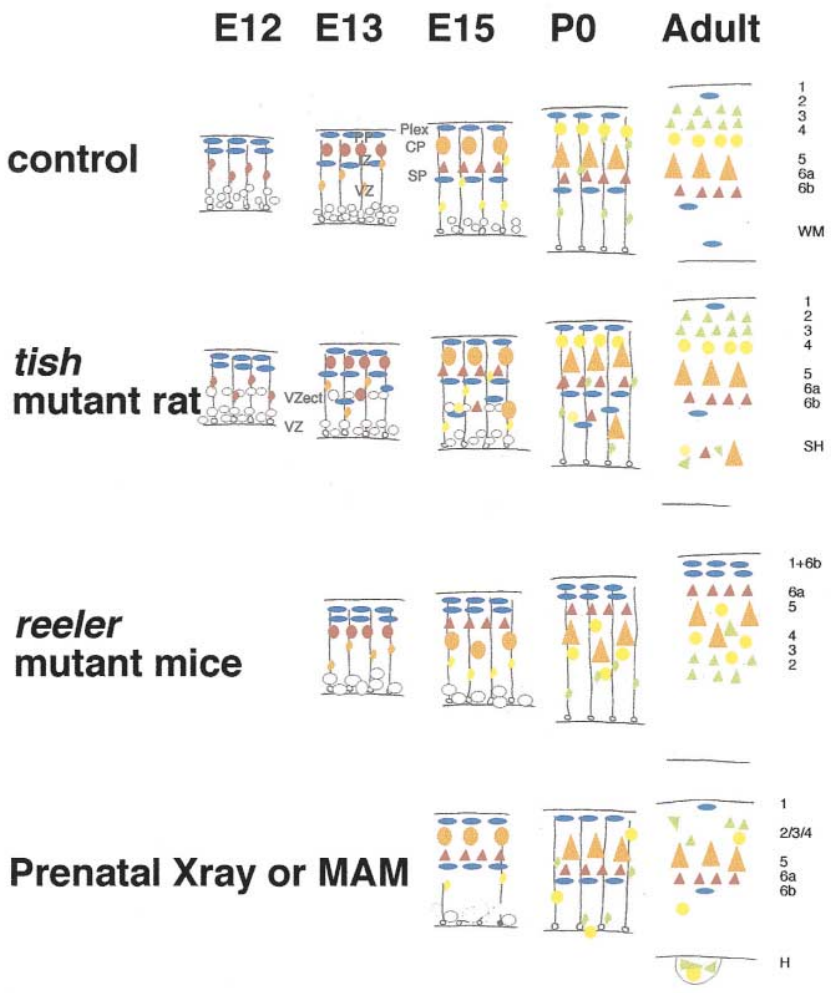


Figure 1. Cortical development in three current rodent models of cortical malformation. The cortical organisation is schematised at embryonic day (E) 12,13, 15, at postnatal day 0 (P0) and in adult control rat, *tish* mutant rat, *reeler* and *reeler*-like mutant mouse and in rats with prenatal treatment at E14–E15 with MAM or irradiation. These examples show that neuronal migration disorders can result from an abnormal neurogenesis (*tish*), a failure of preplate splitting (*reeler*) or a lesion of radial glia (MAM).

an abnormal *heterotopic* position. Absence, interruption or excessive migration will lead neurons to differentiate respectively in a subcortical (i.e. along the ventricle), intracortical (i.e. in the white matter or in an inappropriate layer) or extracortical (i.e. in the submeningeal space) position.

Clinicians have long been interested in the pathophysiology of such displaced neurons, since they have been observed in the brains of patients suffering from epilepsy [32–42] and, more controversially, from schizophrenia [43–47]. The purpose of the present article is to review the literature on the properties of such displaced neurons in animal models in an attempt to clarify their possible contribution to pathophysiological disorders.

## What is a neuronal migration disorder?

### Distinction between variations and errors

Like any complex biological process, cortical migration depicts some interindividual variability that is attributable to slight alterations of the normal process. Indeed, abnormally positioned cortical neurons, that is neurons with a cortical-like morphology situated along their normal migratory pathway, are commonly encountered in the white matter of control brains, especially in young animals as well as in children [48, 49]. These alterations are likely to result from arrest of normal migration, for instance because of obstruction of their migratory path by a blood vessel. These 'developmental' heterotopic neurons tend to be sparser in adults, likely because of their elimination by ontogenetic cell death.

Given the existence of such normally occurring heterotopic neurons, the distinction between normally occurring and pathological heterotopic neurons appears to be difficult. In practice, the distinction mostly relies on the arrangement of heterotopic neurons. Isolated heterotopic neurons are usually considered nonpathologic (but see [50]). By contrast, heterotopic neurons grouped into nodular or band heterotopias are hallmarks of established neuronal migration disorders (fig. 2).

### Not all migration disorders are *migration* disorders

Another problem of definition concerns the mechanistic hypothesis included in the term 'neuronal migration disorder'. The vast majority of experimental NMDs can indeed be attributed to either a failure of neuronal locomotion machinery [51, 52], a disruption of radial glia [30, 53–55] or an alteration of the end migration signalling ([56], reviewed in [57]). These pathological alterations are pure migration disorders, in the sense that they actually result from a disorder of migration.

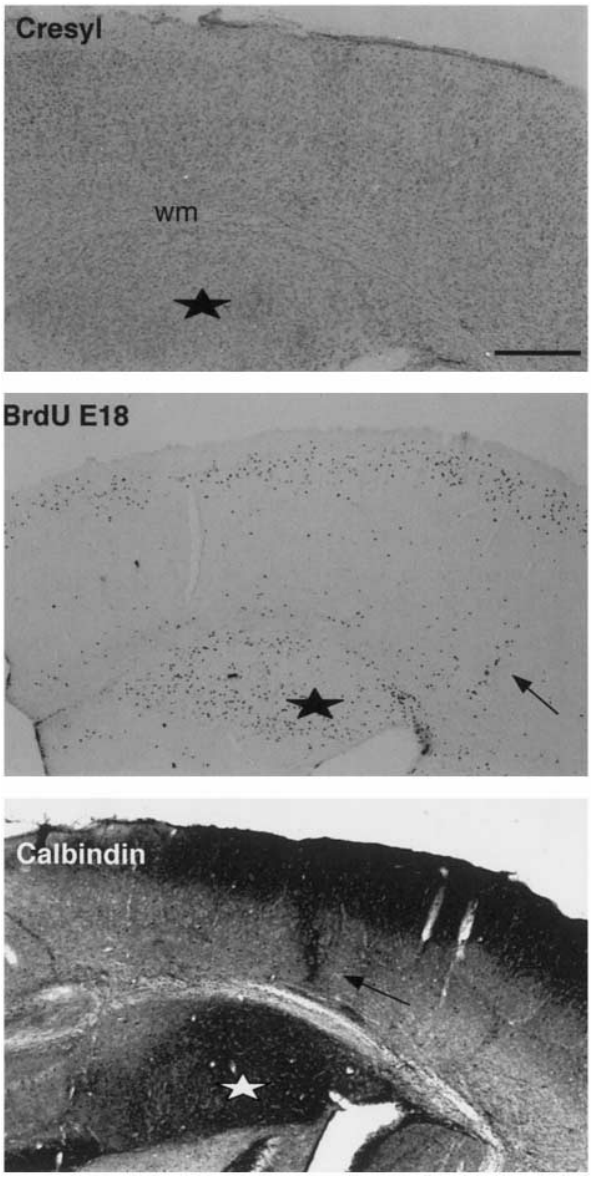


Figure 2. Neuronal migration disorders in rats with prenatal treatment with MAM. (*A*) Cresyl violet-stained section showing a large subcortical heterotopia (star). (*B*) The origin of heterotopic cells can be investigated by immunohistochemical revelation of the S phase marker bromodeoxy uridine (BrdU) injected at E18. This shows that a large number of heterotopic cells, likely normotopic external layer cells, have their last division at E18. Arrow point at a mild NMD, that is a columnar arrangement of neurons born on the same date. (*C*) Immunostaining for calbindin, a calcium-binding protein densely expressed in external layers, confirms the BrdU studies by showing that subcortical heterotopias (star) as well as abnormal columns are densely immunoreactive for calbindin (arrow) as if they were normally situated in the external layers. Scale bar, 500 μm.

However, embryological studies in mutant rodents with NMDs have shown that the perturbation of other de-

velopmental processes can also be involved in the pathogenesis of NMDs. For example, *tish* rat embryos display a second ectopic germinative zone [58], external to the normal periventricular germinative zone (fig. 2B). This second zone can generate neurons that differentiate locally without previous complete migration. Another example involves genetically engineered mice in which CPP32, a gene required for developmental apoptosis, has been disrupted [59]. These mice exhibit periventricular cortical heterotopias which are believed to be formed by excess neurons that failed to migrate—normally these cells would have undergone developmental apoptosis and died during development. Both these examples show that apparent NMDs can indeed result from alterations of neurogenesis prior to migration.

### Endogenous properties of heterotopic neurons

The morphology of heterotopic—mostly subcortical—neurons has been investigated using Golgi impregnations in the prenatal irradiation [60, 61] and MAM [27, 62] models of NMDs. Both pyramidal and nonpyramidal neurons have been identified (fig. 3). Pyramidal neurons have their usual triangular soma, with conserved morphometric parameters [63] and a well-differentiated apical dendrite. However, the dendritic branching pattern appears to be altered, with bent and distorted dendrites. Abnormal neurons are especially conspicuous at the borders of the heterotopia (fig. 3D). Neither a laminated nor a columnar organised structure is observed. The axons of pyramidal neurons course and ramify within the heterotopia, but a substantial number reach the white matter or penetrate the adjacent cortex after a short oblique course. It should be noted that the morphological features of subcortical heterotopic neurons are strikingly similar to those observed in transplants of immature neocortex in adult rat [64–66].

The expression of several proteins has been investigated in a model of intrahippocampal neocortical heterotopia [67, 68] that provides an opportunity to compare the expression of hippocampal (i.e. environmental) and neocortical (i.e. committed) markers in heterotopic neurons. Heterotopic neurons acquire the expression of all investigated cortical markers on the same schedule. By contrast, they fail to express hippocampal markers such as the GluR2 flip subunits of glutamate receptors [69], and the limbic associated membrane protein [68].

Physiological endogenous properties of subcortical heterotopic neurons have also been investigated in subcor-

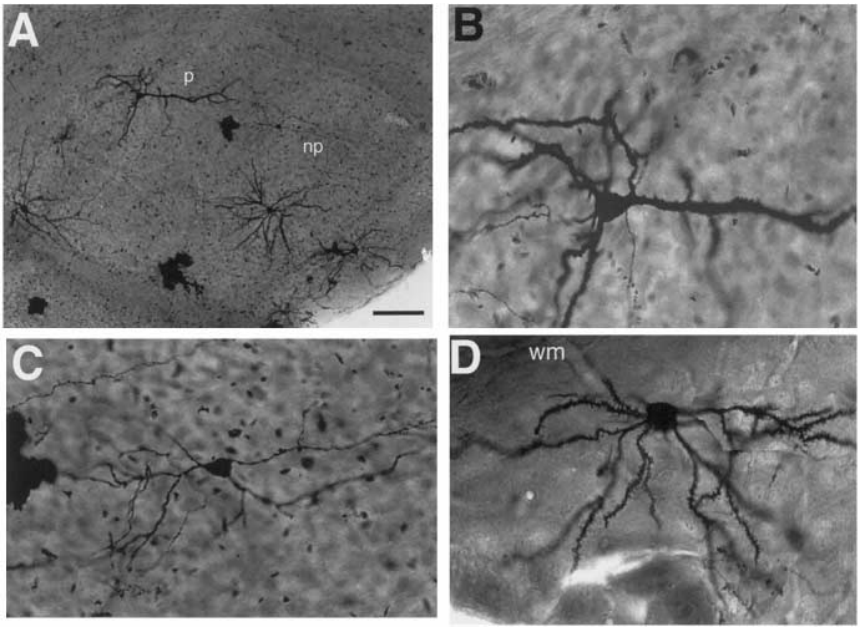


Figure 3. Neuronal morphology in subcortical heterotopias in MAM-treated rats. (*A*) Various cortical neuronal types are recognised in rapid Golgi impregnations in subcortical heterotopias of under the somatosensory cortex such as spiny pyramidal (p) neurons [at higher magnification in *B*] and smooth nonpyramidal (np) neurons (*C*). The abnormal shape of the dendritic tree (note the absence of an apical dendrite) is frequent at the border of the heterotopia (*D*) near the white matter (wm). Scale bar, 100 μm in *A*, 40 μm in *B–D*.

tical heterotopias in the MAM model [63, 70, 71], as well as in the inverted cortex of *reeler* mice [72]. Membrane potential and input resistance values turned out to be similar to those of normotopic neurons, suggesting a wide conservation of these parameters despite the abnormal position of these cells.

These three lines of evidence tend to suggest that heterotopic cortical neurons closely resemble normotopic neurons. Similar conclusions had been drawn from the study of heterotopic cerebellar neurons in mutant mice (reviewed in [72]). However, this claim is somehow tautological. One should be aware of the fact that displaced neurons that would not resemble neocortical neurons could have been missed, especially in unusual position (see below).

## Connections of heterotopic neurons

### Efferent connections

Layer 5 cortical neurons are a major output source of the neocortex, sending axonal projection to subcortical targets such as the spinal cord (in motor areas), the tectum (in visual areas) or the basilar pons. Given this well-described projection pattern, there has been considerable interest in determining the projection targets of displaced layer 5 pyramidal neurons.

Corticospinal neurons identified by retrograde labelling after spinal injection of horseradish peroxidase (HRP) have been observed in subcortical heterotopias after prenatal irradiation [73], in the external neocortical layers after prenatal ethanol treatment [74] or dispersed in the whole cortical thickness in *reeler* mutants [75, 76]. Interestingly, corticospinal neurons situated in the external cortical layers, identified in vivo by their antidromic response to the stimulation of the pyramidal tract, turned out to have a morphology of supragranular neurons [77], reinforcing the previous claim that heterotopic neurons with altered morphology could be underestimated.

These paradigm studies of the corticospinal projection have been extended to other projection systems such as callosal neurons normally encountered in external layers and in layer 5 of the rodent cortex. Callosally projecting neurons were found in subcortical heterotopias in MAM-treated rats [27] and widely dispersed in the cortex of rats prenatally treated with ethanol [78] as well as in *reeler* mice [79]. Subcortical efferent projections have also been described in the large band heterotopias of *tish* mutant rats [80]. Together, these data suggest that heterotopic neurons are able to extend long-range projections and reach the target they would have contacted in normotopic position.

### Afferent connections

There are three main types of afferent systems to the neocortex: monoaminergic fibres from the brainstem, thalamic fibres and cortical fibres from contralateral and associative areas.

To our knowledge, the presence of monoaminergic fibres in subcortical heterotopias has never been investigated. By contrast, thalamic fibres have been shown to contact the large subcortical heterotopias of the *tish* mutant rat [80] as well as the abnormally positioned layer 4 neurons of the cortex of *reeler* mice [81, 82] in an apparently conserved topographical arrangement [13].

The case of corticocortical connections seems to be more complex. Subcortical heterotopias clearly receive cortical connections [83], although their density seems to be smaller than in adjacent normotopic cortex. This could explain the deafferented appearance of subcortical heterotopias when stained for fibres (fig. 4).

The previous examples show that heterotopic neurons can form apparently qualitatively normal connections with fibres afferent to the normotopic cortex. However, they can also form aberrant connections with fibres that normally do not contact the normotopic cortex. One such example was provided by the study of the previously mentioned intrahippocampal cortical heterotopias. Surprisingly, these heterotopic neurons are contacted by the same afferent fibres as the adjacent CA1 neurons, that is the Schaffer collaterals from CA3 [63] and the temporoammonic path from the entorhinal cortex [84]. These connections are formed on distal dendrites of heterotopic neurons since Schaffer collaterals avoid the heterotopic core.

## Heterotopic neurons as a tool to study the specification of axonal projections

There are two ways of looking at axonal pathfinding. One can address either the issue of the developmental decisions that govern the specific behaviour of the different projection neurons or the issue of the molecular mechanisms that guide the growth cone to its target. Both these approaches have been developed using an elegant system of in vitro cocultures (reviewed in [82]). In addition, several investigators have taken advantage of NMDs as a tool to investigate these issues in vivo [85].

The conservation of subcortical projections formed by heterotopic neurons has been interpreted as evidence that cell types are determined by interactions that occur within the ventricular zone, and not by information gained along the migratory pathway or by positional information in the cortex. This view has been reinforced by a recent experiment that was lacking in previous studies: using double labelling, Polleux et al. have inves-

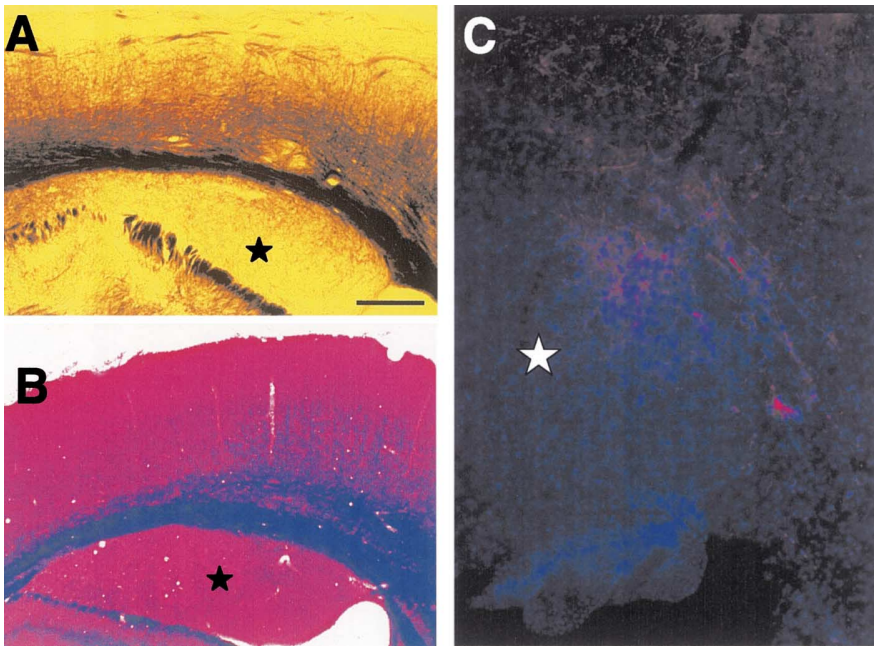


Figure 4. Connections of subcortical heterotopias in MAM-treated rats. Gold staining for fibres (*A*) or myelin (*B*) shows that subcortical heterotopias (star) are sparsely contacted by WM fibres, as compared with the adjacent cortex. However, tracing studies using a cortical injection of carbocyanine reveal neocortical fibres entering the heterotopia, which shows that heterotopias are integrated in the cortical network (*C*). Scale bar, 500 μm in *A*–*B*, 100 μm in *C*.

tigated the correlation between the birth date of neurons (determined by tritiated thymidine injection) and their projection pattern in the adult *reeler* mutant [86]. They found that in *reeler* mutant mice corticospinal neurons are generated over the same 3-day periods as in normals. They conclude that a cell's birth date and its projection sites are closely related, even when migration and laminar environment are altered. However, neurons generated during this period show an increased probability to project to the spinal cord. In the same line, Miller observed an increased number of callosally projecting neurons in the somatosensory cortex of rats with prenatal treatment with ethanol [78]. This could reflect an alteration of either the premigratory instructions given in the ventricular zone or the postmigratory influences exerted in the cortical plate, notably on the pruning of transient axon collaterals [87, 88]. This suggests that even if efferent projections of heterotopic neurons are qualitatively normal, quantitative analysis of their axonal branching would likely reveal abnormalities, including excessive branching and conservation of transient projections.

On the other hand, the study of the afferent projections to heterotopic neurons offers an in vivo tool to investigate the reaction of axons to a displacement of their normal target. The conservation of most afferent projections in subcortical and intracortical heterotopias suggests that heterotopic cortical neurons are able to form normal, at least qualitatively, afferent connections. Similar conclusions had been drawn from the study of the cerebellum of mutant mice. Thus, granule cells heterotopically situated in the external granule layers receive afferent synapses from the mossy fibres in control rats [89, 90] and more strikingly in *weaver* mutant mice [91]. Heterotopic Purkinje cells in *reeler* mice are also contacted by parallel fibres [92]. This was interpreted as evidence of the chemotropic hypothesis that target neurons emit an attractive signal for growing fibres [88]. However, one should be cautious before transposing to normal conditions the lessons from pathological models. For example, an alternative to the chemotropic hypothesis would be that a similar cue, eventually disrupted in pathological conditions, would both guide the cell to its final position and attract its afferent fibres there.

## The pathophysiology of heterotopic neurons

### Neurological deficits in rodents with neuronal migration disorders

Rodents with neuronal migration disorders exhibit various neurological deficits including ataxia in *reeler* mutant mice [23], learning disabilities in rats with prenatal

MAM injection or irradiation [93–95] and seizure disorders or at least cortical hyperexcitability (reviewed in [96]). However, these animals also present other cerebral dysgenesis such as cerebellar atrophy in reeler mice or microcephaly in rats with prenatal MAM. Animal studies therefore could not provide compelling evidence about the precise role of NMDs in neurological disorders (for further discussion, see [97]). Nevertheless, the analysis of the abnormal networks involved in NMDs provides a rational substrate for them, and a way to speculate on the pathophysiological consequences of NMDs. These points constitute the subject of the last section.

### The intraheterotopic network

Very little is known about the functional organisation of the intraheterotopic network. For instance, the organisation of radial interlaminar and tangential intercolumnar connections, the latter being very sensitive to activity-dependant modulation [56], in cortical heterotopias is completely unknown. However, a number of morphological observations suggest that the intraheterotopic network may be organised very differently from the normotopic neocortical network. The first example of this is the ramification pattern of the dendritic tree of heterotopic neurons, which we have seen above to be clearly different from that of normotopic neurons. Given the key role of this parameter in dendritic integration, it is reasonable to suggest that this alteration should have consequences on signal processing by heterotopic neurons.

The second point we would like to emphasise is related to the apparent deafferentiation of heterotopic regions (fig. 4). It is well known that deafferented regions develop a dense network of interconnections that is thought to compensate for the absence of external connections [98]. Morphological evidence for such axonal profusion and disorganisation has been provided by Golgi analysis of human specimens of subcortical heterotopias [99, 100]. Such interconnections may contribute to the synchronisation of neuronal discharges within the heterotopia and putatively to the formation of an epileptogenic focus.

### Heterotopias can form bridges between normally unconnected structures

We have recently defined a pathophysiological mechanism by forming of abnormal networks involving heterotopias using a model of intrahippocampal cortical heterotopias after prenatal treatment with MAM. As discussed above, these heterotopic neurons are contacted by afferent fibres from both the hippocampus and the white matter, while sending their axons to the neocortex. Using electrophysiological recordings in a slice preparation, we demonstrated that these heterotopic neurons have bidirectional connections with the adjacent neocortex, while receiving an excitatory monosynaptic input from hippocampal fibres. A functional consequence of these aberrant connections is that bicuculline-induced paroxysmal activity triggered in the hippocampus can spread directly to the neocortex [63].

Two in vivo observations additionally support the existence of a bridge between the hippocampus and the neocortex in MAM rats. First, focal hippocampal seizure activity induced in vivo by electrical stimulation propagates more frequently to the frontal neocortex in MAM-treated rats than in controls [101]. Second, the increased sensitivity of MAM rats to KA-induced seizures has been shown [102–104] to be associated with a more rapid generalisation of seizure activity monitored by fos immunostaining of the neocortex [105]. Therefore, it would appear that the dual integration of heterotopic neurons into both hippocampal and neocortical circuitry allows the rapid generalisation of hippocampal paroxysmal activity to the neocortex.

## Conclusions

We have shown that heterotopic neocortical neurons mostly resemble normotopic neurons and share with them qualitatively similar morphology, afferent and efferent long-range connections. Anatomical [106, 107] and functional imaging [108–110] in patients with subcortical heterotopias support the view that similar changes also operate in humans.

By contrast, virtually nothing is known about the organisation of the intraheterotopic network. However, quantitative analyses suggest that displaced neurons are altered in some parameters, for instance the dendritic tree or the amount or topography of afferent fibres. This in turn is likely to lead to altered discharge properties which, in combination with the formation of functional bridges between normally unrelated structures, contribute to the pathogenesis of NMD-associated pathologies such as epilepsy.

To conclude, we would like to recall a quotation of Jacobson's textbook on developmental neuroscience [111]. 'Displaced cells persist either because they are integrated into the existing circuitry […] or because they form novel functional systems or extend the functional capabilities of preexisting systems. If variations arise because of mutations whose effects are neutral, or are corrected at later stages of development, they will not be the subject of natural selection but will tend to accumulate.' Our experimental demonstration that heterotopias can form bridges between normally unconnected struc-

tures suggests that one of the mechanisms that eliminates mutations that create new networks involving heterotopic neurons is the consecutive occurrence of pathophysiological disorders such as epilepsy.


1 Sidman R. L. and Rakic P. (1973) Neuronal migration with special reference to developing human brain: a review. Brain Res. **62:** 1–35
2 Raedler E., Raedler A. and Feldhaus S. (1980) Dynamical aspects of neocortical histogenesis in the rat. Anat. Embryol. **158:** 253–269
3 McConnell S. K. and Kaznowski C. E. (1991) Cell-cycle dependance of laminar determination in developing neocortex. Science **254:** 282–285
4 McConnell S. K. (1991) The generation of neuronal diversity in the central nervous system. Ann. Rev. Neurosci. **14:** 269–300
5 Walsh C. A. and Cepko C. L. (1988) Clonally related neurons show several patterns of migration in cerebral cortex. Science **255:** 1342–1455
6 Walsh C. A. and Cepko C. L. (1992) Widespread dispersion of neuronal clones across functional regions of the cerebral cortex. Science **225:** 434–455
7 Reid C. B., Liang I. and Walsh C. A. (1995) Systematic widespread clonal organization in cerebral cortex. Neuron **15:** 299–310
8 Rakic P. (1972) Mode of cell migration to the superficial layers of fetal monkey cortex. J. Comp. Neurol. **145:** 61–84
9 Hatten M. E. (1990) Riding the glial monorail: a common mechanism for glial-guided neuronal migration in different regions of the developing mammalian brain. Trends Neurosci. **13:** 179–184
10 Edmonson J. C. and Hatten M. E. (1987) Glial guided granule neuron migration in vitro: a high-resolution time-lapse video microscopic study. J. Neurosci. **7:** 1928–1934
11 Misson J.-P., Takahashi T. and Caviness V. S. Jr. (1991) Ontogeny of radial and other astroglial cells in murine cortex. Glia **4:** 138–148
12 Komuro H. and Rakic P. (1998) Orchestration of neuronal migration by activity of ion channels, neurotransmitter receptors and intracellular $Ca^{2+}$ fluctuations. J. Neurobiol. **37:** 110–130
13 Fishell G. and Hatten M. E. (1998) Astrotactin provides a receptor system for CNS neuronal migration. Development **113:** 755–765
14 Cameron R. S., Ruffin J. W., Cho N. K., Cameron P. L. and Rakic P. (1997) Developmental expression, pattern of distribution and effect on cell aggregation implicate a neuron-glial junctional domain protein in neuronal migration. J. Comp. Neurol. **387:** 467–488
15 Anton E. S., Cameron R. S. and Rakic P. (1996) Role of neuron-glial junctional domain proteins in the maintenance and termination of neuronal migration across the embryonic cerebral wall. J. Neurosci. **16:** 2283–2293
16 Komuro H. and Rakic P. (1992) Selective role of N-type calcium channels in neuronal migration. Science **257:** 806–809
17 Komuro H. and Rakic P. (1995) Modulation of neuronal migration by NMDA receptors. Science **260:** 95–97
18 D'Arcangelo G., Miao G. G., Chen S.-C., Soares H. D., Morgan J. I. and Curran T. (1995) A protein related to extracellular matrix protein deleted in the mouse mutant reeler. Nature **374:** 719–723
19 Ogawa M., Miyata T., Nakajima K., Yagyu K., Seike M., Ikenaka K. et al. (1995) The reeler gene-associated antigen on Cajal-Retzius neurons is a crucial molecule for laminar organization of cortical neurons. Neuron **14:** 899–912
20 Soriano E., Alvarado-Mallart R. M., Dumesnil N. and Sotelo C. (1997) Cajal-Retzius cells regulate the radial glia phenotype in the adult and developing cerebellum and alter granule cell migration. Neuron **18:** 563–577
21 Frotscher M. (1997) Dual role of Cajal-Retzius cells and reelin in cortical development. Cell Tissue Res. **290:** 315–322
22 Super H., Soriano E. and Uylings H. B. M. (1998) The functions of the preplate in development and evolution of the neocortex and hippocampus. Brain Res. Rev. **27:** 40–64
23 Falconer D. (1951) Two new mutants, 'trembler' and 'reeler', with neurological actions in the house mouse. J. Genet. **50:** 192–201
24 Gonzales J. L., Russo C. J., Goldowitz D., Sweet H. O., Davisson M. T. and Walsh C. A. (1997) Birthdate and cell marker analysis of scrambler: a novel mutation affecting cortical development with a reeler-like phenotype. J. Neurosci. **17:** 9204–9211
25 Oshima T., Ward J., Huh C.-G., Longenecher G., Pant H., Brady R. et al. (1996) Targeted disruption of cyclin-dependant kinase 5 gene results in abnormal corticogenesis, neuronal pathology and perinatal death. Proc. Natl. Acad. Sci. USA **93:** 11173–11178
26 Kwon Y. T. and Tsai L. H. (1998) A novel disruption of cortical development in *p35*(−/−) mice distinct from reeler. J. Comp. Neurol. **395:** 510–522
27 Yurkewicz L., Valentino K. L., Floeter M. K., Fleshman J. W. and Jones E. G. (1984) Effects of cytotoxic deletions of somatic sensory cortex in fetal rats. Somatosensory Res. **1:** 303–327
28 Collier P. A. and Ashwell K. W. S. (1993) Distribution of neuronal heterotopias following prenatal exposure to methylazoxymethanol. Neurotoxicol. Teratol. **15:** 439–444
29 Gressens P., Kosofsky B. E. and Evrard P. (1992) Cocaine-induced disturbances of corticogenesis in the developing murine brain. Neurosci. Lett. **140:** 113–116
30 Gressens P., Lammens M., Picard J. J. and Evrard P. (1992) Ethanol-induced disturbances of gliogenesis and neurogenesis in the developing murine brain: an in vitro and in vivo immunohistochemical and ultrastructural study. Alcohol Alcohol. **27:** 219–226
31 Miller M. W. (1986) Effects of alcohol on generation and migration of cerebral cortex neurons. Science **233:** 1308–1311
32 Fox J. W., Lamperti E. D., Eksioglu Y. Z., Hong S. E., Feng Y., Graham D. A. et al. (1998) Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron **21:** 1315–1325
33 Barkovitch A. J. and Kjos B. O. (1992) Gray matter heterotopias: MR characteristics and correlation with developmental and neurological manifestations. Radiology **182:** 493–499
34 Palmini A., Andermann F., Olivier A., Tampieri D., Robitaille Y. and Andermann E. (1991) Focal neuronal migration disorders and intractable epilepsy: a study of 30 patients. Ann. Neurol. **30:** 741–749
35 Barkovitch A. J., Kuzniecky R. I., Jackson G. D., Becker L. E. and Evrard P. (1996) A classification scheme for malformations of cortical development. Neuropediatrics **27:** 59–63
36 Kuzniecky R. I. and Jackson G. D. (1997) Developmental disorders. In: Epilepsy: A Comprehensive Textbook, pp. 2517–2532, Engel J. Jr. and Pedley T. A. (eds), Lippincott-Raven Publishers, Philadelphia
37 Barth P. G. (1987) Disorders of neuronal migration. Can. J. Neurol. Sci. **14:** 1–16
38 des Portes V., Pinard J.-M., Billuart P., Vinet M.-C., Koulakoff A., Carrié A. et al. (1998) Identification of a novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. Cell **92:** 51–61
39 Eksioglu Y. Z., Scheffer I. E., Cardenas P., Knol J., DiMario F., Ramsby G. et al. (1996) Periventricular heterotopia: an X-linked dominant epilepsy locus causing aberrant cerebral cortical development. Neuron **16:** 77–87
40 Gleeson J. G., Allen K. M., Fox J. W., Lamperti E. D., Berkovic S., Scheffer I. et al. (1998) *doublecortin*: a brain-specific gene mutated in X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. Cell **92:** 63–72

41 Mischel P. S., Nguyen L. P. and Vinters H. V. (1995) Cerebral cortical dysplasia associated with pediatric epilepsy. Review of neuropathological features and proposal for a grading system. J. Neuropathol. Exp. Neurol. **54:** 137–153
42 Robain O. (1996) Introduction to the pathology of cerebral cortical dysplasia. In: Dysplasias of the Cerebral Cortex and Epilepsy, pp. 1–9, Guerrini R., Andermann E., Canapicchi R., Roger J., Zilfkin B. and Pfanner P. (eds), Lippincott-Raven, Philadelphia
43 Jones, E. G. (1995) Schizophrenia and brain development. In: Development of the Cerebral Cortex, pp. 277–295, Ciba Foundation (ed.), Wiley, Chichester
44 Chua S. E. and Murray R. M. (1996) The neurodevelopmental theory of schizophrenia: evidence concerning structure and neuropsychology. Ann. Med. **28:** 547–555
45 Harrison P. J. (1997) Schizophrenia: a disorder of neurodevelopment. Curr. Opin. Neurobiol. **7:** 285–289
46 Weinberger D. R. (1996) On the plausibility of 'the neurodevelopmental hypothesis' of schizophrenia. Neuropsychopharmacol. **14:** S1–S11
47 Raedler T. J., Knable M. B. and Weinberger D. R. (1998) Schizophrenia as a developmental disorder of the cerebral cortex. Curr. Opin. Neurobiol. **8:** 157–161
48 Rojiani A. M., Emery J. A., Anderson K. J. and Massey J. K. (1996) Distribution of heterotopic neurons in normal hemispheric white matter: a morphometric analysis. J. Neuropathol. Exp. Neurol. **55:** 178–183
49 Emery J. A., Roper S. N. and Rojiani A. M. (1997) White matter neuronal heterotopia in temporal lobe epilepsy: a morphometric and immunohistochemical study. J. Neuropathol. Exp. Neurol. **56:** 1276–1282
50 Akbarian S., Kim J. J., Potkin S. G., Hetrick W. P., Bunney W. E. and Jones E. G. (1996) Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. Arch. Gen. Psychiatry **53:** 425–436
51 Baes M., Gressens P., Baumgart E., Casteliet M., Fransen M., Evrard P. et al. (1997) A mouse model of Zellweger syndrome. Nature Gen. **17:** 49–57
52 Faust P. L. and Hatten M. E. (1997) Targeted deletion of the pex2 peroxisome assembly gene in mice provides a model for Zellweger syndrome, a human neuronal migration disorder. J. Cell. Biol. **139:** 1293–1306
53 Miller M. W. (1993) Prenatal exposure to ethanol alters the postnatal development and transformation of radial glia to astrocytes in the cortex. J. Comp. Neurol. **337:** 253–266
54 Zhang L. L., Collier P. A. and Ashwell K. W. S. (1995) Mechanisms in the induction of neuronal heterotopiae following prenatal cytotoxic brain damage. Neurotoxicol. Teratol. **17:** 297–311
55 Roper S. N., Abraham L. A. and Streit W. J. (1997) Exposure to in utero irradiation produces disruption of radial glia in rats. Dev. Neurosci. **19:** 521–528
56 Bolz J. and Castellani V. (1997) How do wiring molecules specify cortical connections? Cell Tissue Res. **290:** 307–314
57 Pearlman A. L., Faust P. L., Hatten M. E. and Brunstrom J. E. (1998) New directions for neuronal migration. Curr. Opin. Neurobiol. **8:** 45–54
58 Lee K. S., Collins J. L., Anzivino M. J., Frankel E. A. and Schottler F. (1998) Heterotopic neurogenesis in a rat with cortical heterotopia. J. Neurosci. **18:** 9365–9375
59 Kuida K., Zheng T. S., Na S., Kuan C.-Y., Yang D., Karasuyama H. et al. (1996) Decreased apoptosis in the brain and premature lethality in CPP32-deficient mice. Nature **384:** 368–372
60 Hicks S. P., D'Amato C. J. and Lowe M. J. (1959) The development of the mammalian nervous system: I. Malformation of the brain, especially the cerebral cortex, induced in rats by radiation. II. Some mechanisms of the malformations of the cortex. J. Comp. Neurol. **113:** 435–469
61 Ferrer I., Xumetra A. and Santamaria J. (1984) Cerebral malformation induced by prenatal X-irradiation: an autoradiographic and Golgi study. J. Anat. **138:** 81–93
62 Dambska M., Haddad R., Kozlowski P. B., Lee M. H. and Shek J. (1982) Telencephalic cytoarchitectonics in the brains of rats with graded degrees of micrencephaly. Acta Neuropathol. **58:** 203–209
63 Chevassus-au-Louis N., Congar P., Represa A., Ben-Ari Y. and Gaiarsa J.-L. (1998) Neuronal migration disorders: heterotopic neocortical neurons in CA1 form a bridge between the hippocampus and the neocortex. Proc. Natl. Acad. Sci. USA **95:** 10263–10268
64 Plashke M., Souphantong M. and Wenzel J. (1995) Morphological alterations of hippocampal pyramidal neurons heterotopically transplanted into the somatosensory cortex of adult rats: a quantitative Golgi study. Anat. Embryol. **192:** 351–361
65 Woodward D. J., Seiger A., Olson L. and Hoffer B. J. (1977) Intrinsic and extrinsic determinants of dendritic development as revealed by Golgi studies of cerebellar and hippocampal transplants. Exp. Neurol. **57:** 984–998
66 Murthy K. S. and Desiraju T. (1989) Quantitative assessment of dendritic branching and spine densities of neurons of hippocampal embryonic tissue transplabnnted into juvenile cortex. Dev. Brain Res. **46:** 33–45
67 Singh S. C. (1977) Ectopic neurons in the hippocampus of the postnatal rat exposed to methylazoxymethanol during fetal development. Acta Neuropathol. **40:** 111–116
68 Chevassus-au-Louis N., Rafiki A., Jorquera I., Ben-Ari Y. and Represa A. (1998) Neocortex in the hippocampus: morpho-functional analysis of CA1 heterotopias after prenatal treatment with methylazoxymethanol in rats. J. Comp. Neurol. **394:** 520–536
69 Rafiki A., Chevassus-au-Louis N., Ben-Ari Y., Khrestchatisky M. and Represa A. (1998) Glutamate receptors in dysplasic cortex: an in situ hybridization and immunohistochemical study in rats with prenatal treatment with methylazoxymethanol. Brain Res. **782:** 142–152
70 Sancini G., Franceschetti S., Battaglia G., Colacitti C., Di Luca M., Spreafico R. et al. (1998) Dysplastic neocortex and subcortical heterotopias in methylazoxymethanol-treated rats: an intracellular study of identified pyramidal neurons. Neurosci. Lett. **246:** 181–185
71 Schwartzkroin P. A., Wenzel H. J., Hochman D. W. and Baraban S. C. (1997) Characterization of heterotopic cell clusters in an animal model of neuronal migration disorders. Epilepsia **38:** S8 (Abstract)
72 Caviness V. S. Jr. and Rakic P. (1978) Mechanisms of cortical development: a view from mutations in mice. Ann. Rev. Neurosci. **1:** 297–326
73 Jensen K. F. and Killackey H. P. (1984) Subcortical projections from ectopic neocortical neurons. Proc. Natl. Acad. Sci. USA **81:** 964–968
74 Miller M. W. (1987) Effect of prenatal exposure to alcohol on the distribution and time of origin of corticospinal neurons in the rat. J. Comp. Neurol. **257:** 372–382
75 Terashima T., Inoue K., Inoue Y., Mikoshiba K. and Tsukuda Y. (1983) Distribution and morphology of corticospinal tract neurons in reeler mouse cortex by retrograde HRP method. J. Comp. Neurol. **218:** 314–326
76 Ikeda Y. and Terashima T. (1997) Corticospinal tract neurons are radially malpositionned in the sensory-motor cortex of the shaking rat *kawasaki*. J. Comp. Neurol. **383:** 370–380
77 Miller M. W., Chiaia N. L. and Rhoades R. W. (1990) Intracellular recording and injection study of corticospinal neurons in the rat somatosensory cortex: effect of prenatal exposure to ethanol. J. Comp. Neurol. **297:** 91–105
78 Miller M. W. (1997) Effects of prenatal exposure to ethanol on callosal projection neurons in rat somatosensory cortex. Brain Res. **766:** 121–128
79 Caviness V. S. Jr. (1976) Patterns of cell and fiber distribution in the neocortex of the reeler mutant mice. J. Comp. Neurol. **170:** 435–448
80 Schotter F., Couture D., Rao A., Kahn H. and Lee K. S. (1998) Subcortical connections of normotopic and heterotopic neurons in sensory and motor cortices of the tish mutant rat. J. Comp. Neurol. **25:** 29–42

81 Terashima T., Inoue K., Inoue Y. and Mikoshiba K. (1987) Thalamic connectivity of the primary motor cortex of normal and reeler mutant mice. J. Comp. Neurol. **257:** 405–421

82 Bolz J., Götz M., Hubener M. and Nowak N. (1993) Reconstructing cortical circuitry in a dish. Trends Neurosci. **16:** 310–316

83 Colacitti C., Sancini G., Franceschetti S., Cattabeni F., Avanzini G., Spreafico R. et al. (1998) Altered connections between neocortical and heterotopic areas in methylazoxymethanol-trated rats. Epilepsy Res. **32:** 49–62

84 Singh S. C. (1978) Redirected perforant and commissural connections of eutopic and ectopic neurons in the hippocampus of methylazoxymethanol-acetate treated rats. Acta Neuropathol. **44:** 197–202

85 Götz M. and Price J. (1994) Cell fate and axonal projection from the cerebral cortex. Sem. Dev. Neurosci. **5:** 359–369

86 Polleux F., Dehay C. and Kennedy H. (1998) Specification of phenotype in cortex: commitment and neurogenesis in the development of corticospinal neurons in *reeler*. J. Neurosci. **18:** 9910–9923

87 Stanfield B. B., O'Leary D. D. M. and Fricks C. (1982) Selective collateral elimination in early postnatal development restricts cortical distribution of rat pyramidal neurons. Nature **298:** 371–373

88 O'Leary D. D. M., Bicknese A. R., De Carlos J. A., Heffner C. D., Koester S. E., Kutka L. J. et al. (1990) Target selection by cortical axons: alternative mechanisms to establish axonal connections in the developing brain. In: Cold Spring Harbor Symposia on Quantitative Biology, pp. 453–468, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York

89 Berciano M. T. and Lafarga M. (1988) Colony forming ectopic granule cells in the cerebellar primary fissure of normal adult rats: a morphologic and morphometric study. Brain Res. **439:** 169–178

90 Lafarga M. and Berciano M. T. (1985) A golgi and morphometric study of the ectopic granule cells of the molecular layer of the rat cerebellum. Brain Res. **345:** 398–401

91 Rakic P. and Sidman R. L. (1973) Organization of cerebellar cortex secondary to deficit of granule cells in weaver mutant mice. J. Comp. Neurol. **152:** 133–162

92 Rakic P. and Sidman R. L. (1972) Synaptic organization of displaced and disoriented cerebellar cortical neurons in reeler mice. J. Neuropathol. Exp. Neurol. **31:** 192

93 Haddad R. K., Rabe A., Laquer G. L., Spatz M. and Valsamis M. P. (1969) Intellectual deficit associated with transplacentally induced microcephaly in the rat. Science **163:** 88–90

94 Rabe A. and Haddad R. K. (1972) Methylazoxymethanol-induced micrencephaly in rats: behavioral studies. Fed. Proc. **31:** 1536–1539

95 Balduini W., Cimino M., Lombardelli G., Abbrachio M. P., Peruzzi G., Cecchini T. et al. (1986) Microencephalic rats as a model for cognitive disorders. Clin. Neuropharmacol. **9:** S8–S18

96 Chevassus-au-Louis N., Baraban S. C., Gaiarsa J.-L. and Ben-Ari Y. (1999) Cortical malformations and epilepsy: new insights from animal models. Epilepsia, in press

97 Rodier P. M. (1980) Chronology of neuron development: animal studies and their clinical implications. Dev. Med. Child Neurol. **22:** 525–545

98 Salin P., Tseng G.-F., Hoffman S., Parada I. and Prince D. A. (1995) Axonal sprouting in layer V pyramidal neurons of chronically injured cerebral cortex. J. Neurosci. **15:** 8234–8245

99 Marin-Padilla M. (1997) Developmental neuropathology and impact of perinatal brain damage. II: White matter lesions of the neocortex. J. Neuropathol. Exp. Neurol. **56:** 219–235

100 Marin-Padilla M. (1996) Developmental neuropathology and impact of perinatal brain damage. I: Hemorrhagic lesions of the neocortex. J. Neuropathol. Exp. Neurol. **55:** 759–773

101 Chevassus-au-Louis N., Ben-Ari Y. and Vergnes M. (1998) Decreased seizure threshold and more rapid kindling in rats with prenatal treatment with methylzoxymethanol. Brain Res. **812:** 422–425

102 De Feo M. R., Mecarelli O. and Ricci G. F. (1995) Seizure susceptibility in immature rats with micrencephaly induced by prenatal exposure to methylazoxymethanol acetate. Pharmacol. Res. **31:** 109–114

103 Germano I. M. and Sperber E. F. (1997) Increased seizure susceptibility in adult rats with neuronal migration disorders. Brain Res. **777:** 219–222

104 Germano I. M. and Sperber E. F. (1998) Transplacentally induced neuronal migration disorders: an animal model for the study of the epilepsies. J. Neurosci. Res. **15:** 473–488

105 Chevassus-au-Louis N., Khazipov R. and Ben Ari Y. (1999) Propagation of limbic seizures: experimental studies. In: Limbic Seizures in Children, Mariani Foundation (ed.), Wiley, London, in press

106 Squier M., Hannan A., Servotte S., Katsnelson A., Blakemore C. and Molnar Z. (1997) Characterization of subcortical neuronal heterotopias in children with epilepsy. Soc. Neurosci. Abstr. **320.15:** 819 (Abstract)

107 Harding B. N. (1996) Gray matter heterotopia. In: Dysplasias of the Cerebral Cortex and Epilepsy, pp. 81–88, Guerrini R., Andermann E., Canapicchi R., Roger J., Zilfkin B. and Pfanner P. (eds), Lippincott-Raven, Philadelphia

108 Li L. M., Cendes F., Bastos A. C., Andermann F., Dubeau F. and Arnold D. L. (1998) Neuronal metabolic dysfunction in patients with cortical malformations: a proton magnetic resonance spectroscopic imaging study. Neurology **50:** 755–759

109 Richardson M. P., Koepp M. J., Brooks D. J., Coull J. T., Grasby P., Fish D. R. et al. (1998) Cerebral activation in malformations of cortical development. Brain **121:** 1295–1304

110 Hatazawa J., Sasjima T., Shimosegawa E., Fujita H., Okudera T., Kanno I. et al. (1996) Regional cerebral blood flow response in gray matter heterotopia during finger tapping: an activation study with positron emission tomography. Am. J. Neuroradiol. **17:** 479–482

111 Jacobson M. (1991) Developmental Neurobiology, Plenum Press, New York