



Review

Mapping form and function in the human brain: the emerging field of functional neuroimaging in cortical malformations

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Received 2 June 2003; revised 12 September 2003; accepted 12 September 2003

Abstract

Malformations of cortical development (MCDs) are increasingly being recognized as a common cause of epilepsy in cases previously felt to be cryptogenic. MCDs occur when the normal process of cerebral cortical development is disrupted, and include disorders of neuronal proliferation, migration, and organization. Many have a genetic basis and the genes responsible for some MCDs have been identified. MCDs represent a unique and valuable substrate in functional brain mapping studies, since as developmental lesions they provide complementary information to studies performed on patients with acquired brain lesions. In recent years an increasing number of functional neuroimaging methods, including positron emission tomography, single photon emission computed tomography, magnetic resonance spectroscopy, and functional magnetic resonance imaging, have been applied to patients with MCDs. In this review we highlight some of the prominent findings in this emerging field by presenting the functional neuroimaging characteristics of selected MCDs.

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Keywords: Malformation; Development; Heterotopia; Functional; Neuroimaging; Mapping; Positron emission tomography; Single photon emission computed tomography; Functional magnetic resonance imaging; Spectroscopy

1. Introduction

The functional organization of the human cerebral cortex has long been a topic of fascination. From the Victorian interest in phrenology to the localizationist movement of clinical neurology, the understanding of what different parts of the brain do has been the subject of much speculation and study. In recent years, the pursuit of functional localization has been revolutionized by the availability of increasingly sophisticated noninvasive functional neuroimaging techniques. The application of these studies both to normal persons and to those with acquired neurological lesions has opened up a new and productive avenue of research into the function of the cerebral cortex.

Although the study of patients with acquired lesions can provide much information on the nature of functional reorganization and plasticity in the adult brain, the study of those with developmental abnormalities offers a complementary approach that allows for functional assessment of the maturing or malformed brain. Malformations of cortical development (MCDs) are disorders in which the normal process of development of the cerebral cortex has been disrupted [1–3]. While some MCDs are detectable by computed tomography (CT), many are more subtle and are seen only on high-resolution magnetic resonance imaging (MRI) or post-mortem examination [1,2]. As neuroimaging methods have improved in recent years, MCDs have been diagnosed more frequently and they are now recognized to be one of the most common diagnoses in children with refractory epilepsy previously felt to be “cryptogenic” [3].

Although a growing number of MCDs have now been characterized anatomically and genetically, there is

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still a relatively more limited understanding of the functional consequences of these developmental disorders [4]. The application of functional neuroimaging techniques to patients with MCDs should yield insights both into the plasticity of the human cerebral cortex and into the functional capacity of developmentally abnormal brain regions [5]. In this article we review a selected number of well-characterized MCDs and present their functional neuroimaging characteristics, emphasizing the most instructive examples of the use of common imaging techniques in these disorders. In addition, we present some of the unanswered questions in this promising new field, including the reliability of interpreting functional neuroimaging results in the setting of disturbed anatomical architecture.

2. Classification of MCDs

MCDs can be classified according to the step in cerebral cortical development that is disrupted in their pathogenesis [6]. The proliferation of neuronal precursors in the ventricular zone of the developing brain is an early step in cortical development. Microcephaly vera and megalencephaly are examples of disorders in which proliferation is abnormally decreased or increased, respectively. The process of neuronal migration from deep proliferative areas to the developing cortical structures at the brain surface occurs over an extended period during gestation, and its disruption can lead to MCDs associated with heterotopia, or misplaced regions of gray matter. Periventricular heterotopia and subcortical band heterotopia (“double cortex”) are both thought to arise from a failure of migration in a subset of neurons. Finally, cortical organization includes such processes as gyration and formation of synaptic connections. Focal cortical dysplasia and gyral abnormalities such as polymicrogyria are typically classified as disorders of organization. It is important to recognize that these processes are not temporally discrete and in fact occur during overlapping periods in brain development. In addition, the genes that disrupt cortical development may act on more than one of these

processes. Finally, for some MCDs, the mechanism of their developmental pathogenesis is still unclear, rendering their classification by this scheme tentative.

3. Periventricular heterotopia

3.1. Clinical and radiological features

Bilateral periventricular nodular heterotopia (BPNH) is a disorder of neuronal migration in which heterotopic nodules of neurons line the ventricles of the brain in a symmetrical fashion [7]. These nodules have the signal intensity of gray matter on MRI sequences and can protrude into the ventricular lumen (Fig. 1). Clinically, patients with BPNH typically present with seizures, either partial or generalized, that begin in adolescence. Most patients have normal intelligence and no other neurological problems besides epilepsy.

3.2. Genetic and molecular basis

Most commonly, BPNH is an X-linked dominant disorder seen in females and is associated with mutations in the filamin A gene (FLNA) [8]. Filamin A is an intracellular actin-crosslinking protein that is essential for cell locomotion, among other functions [9]. The leading hypothesis of BPNH pathogenesis is that neurons expressing the mutant allele fail to migrate properly away from the ventricular zone, resulting in the presence of the heterotopic nodules. Due to X inactivation, a subset of neurons in heterozygous females fail to migrate, while the remainder migrate properly to the cortical surface. Males who are hemizygous for the mutant allele die prenatally of causes that are not clear but may relate to a vascular or coagulation defect.

3.3. Functional neuroimaging

BPNH is an attractive MCD on which to perform functional studies, since the normal neurological function of most patients allows them to cooperate easily

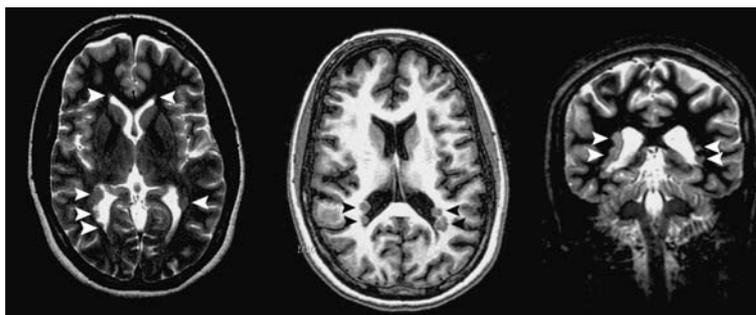


Fig. 1. Magnetic resonance imaging (MRI) appearance of periventricular heterotopia. T2-weighted axial, T1-weighted axial, and T2-weighted coronal images demonstrate the periventricular nodules (arrowheads) that are isointense to gray matter on all sequences and line the ventricular walls, sometimes protruding into the lumen.

with specified tasks. Remarkably, despite this normal level of function, BPNH is characterized by one of the most dramatic alterations of cortical architecture, since vast numbers of neurons are separated from their usual location and synaptic partners by distances of centimeters. Moreover, the heterotopic neurons lack the normal lamination of the cerebral cortex. These architectural disruptions beg the question of whether the heterotopic neurons are functionally connected to the normal cortex and whether they might actually have a role in volitional behavior. Thus far, the evidence is not clear.

In one study, positron emission tomography (PET) scanning using [^{18}F]fluoro-2-deoxy-D-glucose (FDG) and single photon emission computed tomography (SPECT) scanning using technetium-99m-hexamethylpropyleneamine oxime (HMPAO) demonstrated that glucose metabolism and perfusion in the heterotopic nodules in BPNH appeared to be almost identical to that in normal cerebral cortex [10], suggesting that the nodules might have rates of physiological activity comparable to those of normal cortical regions. Another study employed H_2^{15}O PET in MCD patients to investigate changes in regional cerebral blood flow (rCBF) while patients were asked to perform certain tasks. In two cases of periventricular heterotopia, there was some evidence that rCBF was focally increased in the heterotopic nodules as well as in overlying cortex during task performance [11], suggesting that the nodules may have functional connections with the overlying cortex, assuming that these rCBF changes represent reactive hyperemia in response to increased neuronal activity. Although such PET and SPECT evidence is suggestive, the relative limitations in spatial resolution raise questions about how well these techniques can be relied on to study heterotopic nodules that can be less than a centimeter in diameter.

Magnetic resonance spectroscopy (MRS) is a noninvasive MRI-based technique that allows for the quantification of biochemical metabolite concentrations within specified brain regions. In two MRS studies of MCD patients, including nine total patients with periventricular heterotopia, heterotopic lesions showed a relative decrease in *N*-acetylaspartate (NAA) in most cases, suggesting loss of neuronal function [12,13]. In one study the NAA/creatine (Cr) ratio was decreased in a region extending beyond the borders of the anatomically defined malformation, suggesting that neuronal metabolic dysfunction was present even outside the visible lesion [12]. Another MRS study, however, demonstrated altered metabolite concentrations in focal cortical dysplasias but not in gray matter heterotopias, although only one patient with periventricular heterotopia was studied [14]. One particular concern with the use of MRS in this disorder is the need to ensure that partial cerebrospinal fluid (CSF) volume effects are corrected for in the quantification of metabolite con-

centrations, since the nodules abut the ventricular lumen. Overall, the evidence is thus conflicting as to whether the heterotopic nodules in BPNH have a biochemical composition consistent with regions of normally functioning neurons.

The fact that most BPNH patients have normal cognitive function, coupled with the striking presence of these periventricular nodules containing large numbers of neurons, raises the possibility that these nodules may be functionally active. However, if they truly are involved in cognitive activity, it would imply a plasticity of circuits that is remarkable. Although the PET, SPECT, and MRS studies described above can provide supportive evidence regarding the heterotopic nodules' *capacity* for functional activity based on perfusion patterns, metabolic rates, and biochemical composition, functional MRI can more definitively answer the question of whether the nodules actually become activated in response to a functional paradigm.

4. Subcortical band heterotopia (“double cortex”)

4.1. Clinical and radiological features

Subcortical band heterotopia (SBH) is a disorder of neuronal migration characterized by a band of heterotopic gray matter that is present in the white matter between the cortical mantle and the ventricles [15]. Clinically, most patients suffer from developmental delay and epilepsy. Mental retardation can range from absent to severe, and seizures can be of multiple different types, including complex partial, generalized tonic-clonic, absence, and even infantile spasms [16].

4.2. Genetic and molecular basis

SBH is an X-linked dominant disorder associated with mutations in the *DCX/XLIS* gene [17,18]. This gene encodes doublecortin, a microtubule-associated protein that appears to be important in cell locomotion. As in BPNH, females heterozygous for the mutant *DCX/XLIS* allele demonstrate a phenotype associated with migration failure in a subset of neurons (SBH), while males who are hemizygous for the mutant allele have a more severe brain malformation called lissencephaly (discussed below).

4.3. Functional neuroimaging

Despite the cognitive deficits in most patients with SBH, this disorder has been the subject of several functional imaging studies that have successfully addressed the question of whether misplaced regions of gray matter can become functionally activated. Several older FDG-PET studies in patients with SBH and

epilepsy, which demonstrated either normal or increased glucose metabolism in the heterotopic band of gray matter [19–21], have long raised the possibility of normal physiological activity in the heterotopic neurons, although they are subject to the same spatial resolution limitations mentioned earlier. More recently, a number of case reports of blood oxygenation level-dependent (BOLD) fMRI in SBH have provided more tantalizing evidence [22–24]. In several patients studied, performance of a motor task resulted in activation of both the overlying motor cortex and the corresponding segment of the heterotopic band. Of two patients studied using a visual stimulation paradigm, one demonstrated a normal pattern of occipital cortex activation, while in the other patient the BOLD activation extended along a line from the occipital cortex toward the ventricular wall, as if paralleling the route of neuronal migration during development [23].

These findings indicate that the heterotopic band in SBH can become activated in association with functional tasks; however, the question of whether the heterotopic region is *essential* for the performance of these tasks cannot be answered by this technique. Interestingly, the focal activation seen in these studies supports the possibility that a regional specificity to the functional role of heterotopia exists that parallels the regional specificity of cerebral cortex function.

These and other fMRI results must be interpreted with the understanding that the exact relationship between BOLD activation and neuronal activity is still unclear; it is generally assumed that BOLD changes, which result from differing MRI signals of oxyhemoglobin and deoxyhemoglobin, represent local alterations in perfusion that occur in direct response to increases in neuronal activity, but other explanations are possible [25]. With regard to MCD studies in particular, it is possible that BOLD signal changes may be atypical and more difficult to interpret in tissue lacking normal cortical architecture and organization. This may be of particular concern in focal malformations with associated vascular anomalies, since abnormal venous drainage patterns may serve to alter BOLD signal in unpredictable ways.

5. Polymicrogyria

5.1. Clinical and radiological features

Polymicrogyria (PMG) is an MCD characterized by an excessive number of small gyri with abnormal cortical lamination [1]. PMG is generally felt to be due to a disruption in cortical organization. Radiologically, the diagnosis of PMG has been clarified significantly by the availability of high-resolution MRI. Because the cortical surface in PMG can often appear smooth on neuro-

imaging, resembling pachygyria, the key to diagnosis rests on the irregular, scalloped appearance of the gray–white junction on high-resolution MRI [26]. The clinical consequences of PMG depend on the location and distribution of the malformation [27].

5.2. Genetic and molecular basis

Although PMG can arise from a number of different etiologies, including environmental insults during gestation, the presence of bilateral symmetric PMG often suggests a genetic etiology, and several such syndromes have been described [28]. Bilateral perisylvian PMG (BPP) [29] appears to be genetically heterogeneous, although a locus on the X chromosome has been identified in some families [30]. Bilateral frontoparietal PMG (BFPP), an autosomal recessive disorder characterized clinically by developmental delay, seizures, dysconjugate gaze, and cerebellar signs, is caused by an autosomal recessive gene localized to chromosome 16q [31,32]. A disorder of bilateral generalized polymicrogyria appears to be clinically and genetically distinct from BFPP and has presumed autosomal recessive inheritance (Chang et al., unpublished).

5.3. Functional neuroimaging

A number of noninvasive neuroimaging studies of PMG patients have attempted to identify the metabolic characteristics of polymicrogyric tissue. In a FDG-PET study of perisylvian dysgenesis patients (most with clear polymicrogyria), a majority had normal gray matter metabolic patterns in the anatomically abnormal perisylvian areas, while a minority had a heterogeneous pattern of hypometabolism [33]. An MRS study that included three patients with focal forms of PMG found that two demonstrated low NAA within the lesion and two demonstrated low NAA or a low NAA/Cr ratio in the perilesional area [34]. However, another study including a patient with right frontal PMG and another with bilateral occipital PMG found no MRS abnormalities within the polymicrogyric tissue in either case [14]. Similarly, three patients with BPP had no significant NAA/Cr changes within the polymicrogyric lesion or perilesional area [12]. Taken together, the results of these studies and other case reports suggest that there is no consistent metabolic “signature” to regions of polymicrogyria, based on glucose metabolism and biochemical metabolite concentrations. Even when metabolic abnormalities are seen, their geographic extent relative to the anatomical malformation can differ.

BOLD-fMRI has been described in a patient with bilateral parasagittal parieto-occipital PMG, a well-described sporadic syndrome [35]. In this case, visual stimulation with a pattern-reversal checkerboard stimulus resulted in fMRI activation of the polymicrogyric

cortex, suggesting that the malformed regions might play a role in processing visual information [36], although the usual caution in interpreting BOLD-fMRI results in MCDs is warranted. Given the conflicting PET and MRS results, as well as the fact that PMG is clinically quite heterogeneous, further fMRI studies are needed to confirm this finding and to characterize more fully the functional neuroimaging of this disorder.

6. Schizencephaly

6.1. Clinical and radiological features

Schizencephaly is a brain malformation characterized by a cleft through the cerebral hemisphere that extends from the pial surface to the ependymal surface and is usually lined with cortex that is dysplastic, often polymicrogyric [2,37]. Schizencephaly is radiologically divided into a “closed-lip” form, in which the two sides of the cleft are apposed, and an “open-lip” form, in which they are not. Clinical features depend on the location and extent of the malformation: Those with the unilateral closed-lip form often have a mild focal neurological deficit, if any, and a low probability of seizures, while those with the bilateral open-lip form can suffer from severe developmental delay and refractory epilepsy [37].

6.2. Genetic and molecular basis

Most cases of schizencephaly, especially when unilateral, are not genetic and are likely caused by an environmental insult during gestation that leads to an encephaloclastic, or destructive, process. Some cases of bilateral schizencephaly, however, have been associated with mutations in the *EMX2* gene, a homeobox gene that is thought to play an important role in the development of the rostral forebrain [38].

6.3. Functional neuroimaging

Unilateral schizencephaly has served as an excellent substrate for brain mapping studies by investigators seeking to establish the extent of functional plasticity in the presence of focal developmental malformations. A number of BOLD-fMRI studies have shown that motor control of a limb can reside in ipsilateral frontal cortex when the contralateral cortex is schizencephalic [39–41], thus indicating a significant degree of plasticity. In contrast, one fMRI study of a right-handed patient with an asymptomatic left frontal schizencephaly demonstrated that the dysplastic neuronal tissue lining the cleft and the adjacent cortex were activated during a language task, suggesting that the malformed region may actually participate in physiological cerebral function [42]. The fact that FDG-PET and HMPAO-SPECT

scanning has shown that the walls of schizencephalic clefts demonstrate normal gray matter metabolism and perfusion also suggests the potential for retained physiological function in these areas [43]. The focal nature of schizencephaly and the relatively straightforward identification of clefts on anatomical neuroimaging (compared with subtle focal cortical dysplasias, for example) will continue to make this a useful MCD for studies of functional plasticity.

7. Classical lissencephaly

7.1. Clinical and radiological features

Lissencephaly is a term that encompasses two different cortical malformations both characterized by the appearance of a smooth brain surface. In classical lissencephaly, the cortex usually exhibits four layers and an absence of normal gyri and sulci [44,45]. Classical lissencephaly essentially represents the most severe and widespread form of pachygyria, a term that indicates the presence of broad gyri and a simplified sulcal pattern. Clinically, patients suffer from profound mental retardation, cerebral palsy, and epilepsy. Cobblestone lissencephaly, usually seen in association with congenital muscular dystrophy, is a different disorder in which the leptomeningeal barrier is defective and glioneuronal heterotopia are seen microscopically on the brain surface, having apparently migrated beyond the pia [46].

7.2. Genetic and molecular basis

Two responsible genes have been identified for classical lissencephaly in its isolated form: *DCX/XLIS* (discussed earlier) and *LIS1*, located on chromosome 17p. While mutations in both genes lead to generally similar clinical features, some radiological features appear to help distinguish between the two [47]. Miller–Dieker syndrome, which includes severe classical lissencephaly and facial dysmorphism, results from a 17p deletion that includes *LIS1* and neighboring genes [48].

7.3. Functional neuroimaging

Multiple functional studies have been performed in children with classical lissencephaly, although the significant cognitive deficits associated with this disorder in its most widespread form have limited the usage of fMRI in these patients. FDG-PET scans on eight children with isolated lissencephaly demonstrated a bilaterally symmetric pattern of cortical glucose metabolism characterized by two layers, with the inner layer demonstrating higher metabolic rates than the outer layer [49]. This finding is similar to results in fetal sheep, leading to speculation that these layers may represent the metabolic

state of the cerebral cortex before extensive dendritic development or synaptic formation has occurred.

In an HMPAO-SPECT study performed on 13 classical lissencephaly patients, focal or multifocal hypoperfusion was seen in most patients but the areas of hypoperfusion did not correlate well with the distribution of the cortical malformation on anatomical images [50]. In another study, ^{133}Xe -SPECT scanning in 14 children with classical lissencephaly demonstrated that frontal rCBF was increased in these subjects compared with controls [51]. Furthermore, this pattern did not change with age, unlike perfusion patterns in normal brains, raising the possibility of an impairment in postnatal maturation. In summary, classical lissencephaly in its generalized form appears to demonstrate widespread metabolic and perfusion-related abnormalities that may be consistent with delayed or arrested cortical maturation.

fMRI has been reported in a patient with lissencephaly limited to the temporo-occipital regions bilaterally [52]. When this patient was asked to perform a visual confrontation naming task, islands of activation were seen in the lissencephalic cortex homologous to visual association regions activated in normal subjects performing the same task. This evidence provides further support for the hypothesis that regions of even severely malformed cortex may not only become functionally activated in response to a particular stimulus but may also retain their regional specificity of function despite their disrupted development and abnormal architecture.

8. Conclusions

MCDs are a unique substrate for functional brain mapping studies using modern neuroimaging techniques. They provide information about developmental maturation and plasticity that cannot be acquired from studies of normal persons or those with acquired neurological lesions. Their phenotypic range raises questions about the ability of malformed regions to maintain their usual capacity and specificity of function and to participate in their usual network connections. However, the results to date from functional studies of these disorders are at times conflicting and still incomplete. Several key questions remain unanswered.

8.1. Do regions of malformed cortex retain a functional role in brain activity?

The evidence is mixed. It likely depends to a significant extent on the severity and distribution of the malformation or on the usual functional role subserved by the affected region of cortex. There are conflicting PET, SPECT, and MRS results regarding the question of

whether regions of malformed cortex demonstrate metabolic or perfusion-related patterns consistent with normally functioning gray matter. However, the most direct and compelling evidence comes from the multiple fMRI studies that have demonstrated BOLD activation in anatomically malformed tissue. The interpretation of these findings, though, must be tempered by a recognition that our understanding of the relationship between BOLD signal and neuronal activity, especially in architecturally abnormal areas, is still imprecise.

8.2. Do regions of heterotopic gray matter have a functional role in brain activity?

There is certainly some evidence, mostly from fMRI studies in SBH, to suggest that heterotopic gray matter may become functionally activated during the performance of certain tasks, and that this pattern of activation may demonstrate a regional specificity that parallels the regional specificity of cerebral cortical function. SBH, however, is characterized by a heterotopic band that is fairly anatomically close to the overlying cortex; it remains to be seen whether similar findings will be seen in BPNH, in which the heterotopic nodules are many centimeters distant from the cortex (and appear to show MRS evidence of neuronal dysfunction in some studies). Although the phenotype of normal cognitive function in BPNH supports the plausibility of functioning heterotopic nodules, the extent to which the usual neuronal circuitry would have to be altered for this to take place would be remarkable.

8.3. To what extent is there functional plasticity in the developing cerebral cortex when congenital malformations are present?

The functional neuroimaging evidence suggests that at least in some cases, the usual functions of a malformed cortical region may “relocate” to other areas, even in the contralateral hemisphere. This has most prominently been demonstrated in fMRI studies of schizencephaly. The extent of this plasticity likely depends on the specific nature, location, and severity of the developmental disruption. (For example, less severely malformed cortex, such as seen in polymicrogyria, may retain its usual function, as described above.) In the future, the use of other investigative methods, both invasive and noninvasive, including transcranial magnetic stimulation and direct stimulation during electrocorticography, may provide insight into issues of functional plasticity as well.

Acknowledgments

B.S.C. is supported by the Clinical Investigator Training Program: Beth Israel Deaconess Medical

Center–Harvard/MIT Health Sciences and Technology, in collaboration with Pfizer Inc. C.A.W. is an Investigator of the Howard Hughes Medical Institute and is supported by NINDS (R37 NS35129) and the March of Dimes (6-FY00-132).

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