Perisylvian dysgenesis
Clinical, EEG, MRI and glucose metabolism features in 10 patients

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Summary
We studied 10 patients who had neurological disorders with a MRI-based diagnosis of perisylvian dysgenesis based on the fact that the parasagittal and centrifugal extremity of the sylvian fissure was abnormally mesial. This abnormality was bilateral in seven cases; in the other three patients, the contralateral sylvian fissure appeared either normal (two cases) or enlarged (open operculum). The perisylvian cortex had a polymicrogyric appearance in most patients. Potential aetiopathogenic factors were determined in four patients. In two of them, ischaemia at mid-gestation was ascribed to death of a co-twin in a context of monozygotic twinning. In the other two patients, who were siblings, genetic factors were suspected. Pseudobulbar palsy was found in eight patients and epilepsy in five patients. We used PET with [18F]fluorodeoxyglucose to test the hypothesis that, despite this clinical and MRI heterogeneity, regional cerebral glucose distribution could have common features in these patients. The analysis of PET data was performed by visual inspection in two cases and by using statistical parametric mapping (SPM) in eight patients compared with a control group. Segmented grey matter MRIs of seven out these patients were also analysed using SPM. We found that the abnormal perisylvian cortex had normal grey matter activity in eight patients and in the other two there was a heterogeneous pattern with areas of preserved metabolism and of decreased metabolism. Metabolic changes were also detected outside the polymicrogyric-like cortex; three patients had hypometabolic areas in cortical regions where the MRI appeared normal and had a normal intensity. When polymicrogyria extended into the white matter, this ectopic dysgenetic cortex was associated with a grey matter pattern within the white matter territory, and was detected by SPM as areas of PET hypermetabolism and MRI hyperintensity. In order to detect possible metabolic changes undetected by the individual analyses, the group of patients was compared with the control group. This comparison revealed bilateral hypometabolism in the frontal opercular cortex. We propose that these PET data be considered in light of the presumed cyto-architectonic pattern of perisylvian dysgenesis, i.e. polymicrogyria. In this malformation, two dense cell layers are separated by a necrotic sparse cell layer. We speculate that the amount of synaptic activity preserved in these dense cell layers depends on the importance and timing of the necrotic process; this hypothesis accounts for the large range of metabolic patterns found, from profoundly decreased glucose metabolism to nearly normal activity.

Keywords: polymicrogyria; cortical dysgenesis; PET; glucose metabolism; MRI

Abbreviations: FDG = [18F]fluorodeoxyglucose; SPM = statistical parametric mapping

Introduction
Inherited or prenatally acquired disturbances of the neuronal migration and gyration processes are associated with various abnormalities of cortical organization (Barth, 1987; Barkovich et al., 1992). Raymond et al. (1995) have proposed the term ‘cortical dysgenesis’ for this heterogeneous group of cerebral malformations. Since the availability of CT and MRI, a number of subcategories and syndromes have been identified according to clinical and radiological criteria (Palmini et al., 1998).
Polymicrogyria refers to an abnormal gyration characterized by narrow and crowded gyri; this pattern can be difficult to distinguish from pachygyria on imaging, since the surfaces of the many small gyri may fuse, resulting in a macroscopic appearance similar to pachygyria (Titelbaum et al., 1989; Shevell et al., 1992; Kuzniecky et al., 1993; Routon et al., 1994). Polymicrogyria is characterized by narrow and crowded gyri; this pattern can be difficult to distinguish from pachygyria on imaging, since the surfaces of the many small gyri may fuse, resulting in a macroscopic appearance similar to pachygyria (Titelbaum et al., 1989; Becker, 1990; Barkovich et al., 1992; Aicardi, 1994; Raymond et al., 1995). Nevertheless, high-definition MRI may show subtle signs (irregular brain surface, irregular transition into the white matter, cortical thickness not exceeding 5–7 mm, focal atrophy and asymmetry) which support a diagnosis of polymicrogyria (Barkovich et al., 1993) according to essential diagnostic criteria (oropharyngoglossal dysfunction, dysarthria and bilateral perisylvian malformations on imaging) and secondary criteria (including mental retardation and epilepsy). Post-mortem examinations have demonstrated polymicrogyria in these patients (Becker et al., 1989; Shevell et al., 1992; Kuzniecky et al., 1993; Routon et al., 1994).

For the analysis of MRI data, we used a control group of 21 normal volunteers aged 20–40 years. All subjects gave informed consent to participate. The study was approved by the ethics committee of the Erasme Hospital.

MR imaging
MRI was performed on a 0.5-T unit for Patients 1, 7 and 8, and on a 1.5-T unit for the other patients. Spin echo (T1-weighted, proton density and T2-weighted) and inversion recovery sequences were performed in the sagittal, axial and coronal planes. In all but Patients 1 and 2, three-dimensional T1-weighted [3D-FE (field echo) imaging] images of 1–2 mm thickness were obtained.

For the control group, MRI was performed on a 1.5-T unit; 3D-FE sequences were used to produce 1.3-mm-thick images in the axial plane.

PET imaging
PET scans were obtained using a CTI-Siemens 933 camera with eight rings of detectors providing fifteen 6.75-mm-thick slices. All patients fasted for ≥4 h, and received an intravenous dose of 120 MBq of FDG, adapted to the patient’s weight. One patient (Patient 2) was sedated with pentobarbital (5 mg/kg) given intrarectally 1 h before PET examination. Five patients were taking anti-epileptic drugs (Patient 4, hydantoin plus lamotrigine; Patients 5 and 10, carbamazepine plus vigabatrin; Patient 8, hydantoin plus phenobarbital; and Patient 9, hydantoin). All PET studies were done interictally; in Patients 4, 5, 9 and 10, the EEG was monitored during the PET procedure. The PET slices were obtained parallel to the canthomeatal line.

Analysis of PET and MRI data
Analysis was performed on a SPARC workstation (Sun Microsystems Inc., Surrey, UK) using the software developed for statistical parametric mapping (SPM), version 96 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London), implemented in MATLAB (Mathworks, Sherborn, Mass., USA).

Spatial normalization
PET and MR images were transformed into a standard anatomical space which conformed with the space described in the proposal by the Ethics Committee of the Erasme Hospital.
Table 1  Summary of clinical, EEG and MRI data for the 10 patients

<table>
<thead>
<tr>
<th>Patient/sex/age (years)</th>
<th>History</th>
<th>Epilepsy onset; type</th>
<th>Neurological examination of seizure</th>
<th>EEG</th>
<th>MRI: side of perisylvian dysgenesis*, associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/2</td>
<td>Monochorial twin pregnancy; death of co-twin at 16–18 weeks</td>
<td>None</td>
<td>Developmental delay, spastic diplegia, dysarthria</td>
<td>Normal</td>
<td>R and L, subcortical parieto-temporo-occipital atrophy</td>
</tr>
<tr>
<td>2/M/3</td>
<td>Unremarkable</td>
<td>None</td>
<td>Developmental delay, pseudobulbar palsy</td>
<td>Normal</td>
<td>R and L</td>
</tr>
<tr>
<td>3/F/5</td>
<td>Hydramnios</td>
<td>None</td>
<td>Severe pseudobulbar palsy, feeding with gastrostomy</td>
<td>Bilateral occipital SSW suppressed by eye opening</td>
<td>R and L</td>
</tr>
<tr>
<td>4/F/6</td>
<td>Unremarkable</td>
<td>3 months; atypical absences, atomic seizures</td>
<td>Pseudobulbar palsy and spastic quadriparesis (R &gt; L), IQ = 74</td>
<td>Multifocal SSW (R and L centrotemporal area), generalized SSW</td>
<td>L, marked frontal and parietal extension of cortical dysgenesis</td>
</tr>
<tr>
<td>5/F/8</td>
<td>Monochorial twin pregnancy; death of co-twin at mid-gestation</td>
<td>4 years; atypical absences</td>
<td>Microcephaly, severe pseudobulbar palsy and spastic quadriplegia</td>
<td>Slow dysrhythmia, generalized SSW</td>
<td>R and L, corticocortical parieto-temporo-occipital atrophy</td>
</tr>
<tr>
<td>6/M/13</td>
<td>Born at 28 weeks of gestation with a weight of 1820 g</td>
<td>None</td>
<td>Severe pseudobulbar palsy, discrete L arm paresis, PQ = 81</td>
<td>R centro-temporal focus of spikes</td>
<td>R, L open sylvian fissure with upper temporal atrophy</td>
</tr>
<tr>
<td>7/M/13</td>
<td>Unremarkable</td>
<td>None</td>
<td>Pseudobulbar palsy, spastic quadriplegia, IQ = 90</td>
<td>R and L centro-temporal focus of spikes</td>
<td>R and L</td>
</tr>
<tr>
<td>8/M/22 (Patient 10)</td>
<td>First degree affected</td>
<td>13 years; somatosensory seizures of L arm</td>
<td>Discrete L inferior facial paresis</td>
<td>R fronto-parietal focus of sharp and slow waves</td>
<td>R</td>
</tr>
<tr>
<td>9/F/30</td>
<td>Unremarkable</td>
<td>25 years; somatosensory seizures of R leg</td>
<td>Dysarthria, discrete R paresis and hypoesthesia, IQ = 66</td>
<td>Diffuse slow dysrhythmia</td>
<td>R and L, bilateral clefts and absence of septum pellucidum</td>
</tr>
<tr>
<td>10/F/32</td>
<td>First degree affected (Patient 8); neonatal asphyxia</td>
<td>1 year; clusters of spasms, atomic seizures, CPS</td>
<td>L congenital hemiparesis, IQ = 55</td>
<td>Multifocal spikes with R temporal predominance, generalized SSW</td>
<td>R and L, R perirolandic dysgenesis</td>
</tr>
</tbody>
</table>

M = male; F = female; R = right; L = left; IQ = intelligence quotient; PQ = performance quotient; CPS = complex partial seizures; SSW = spikes and slow waves. *P < 0.05 for the x-axis coordinate of the parasagittal and centrifugal extremity of the sylvian fissure compared with control subjects (see text and Fig. 1).

in the atlas of Talairach and Tournoux (1988). Affine and non-linear transformations were applied, as proposed by Friston et al. (1995a), to produce spatially normalized images. For MRI, two sets of images composed of 1 and 2 mm cubic voxels were obtained; voxel resolution of spatially normalized PET images was 2 mm. However, this procedure was not achieved in PET images of Patients 1 and 5, for which profound morphological cortical changes precluded accurate spatial normalization, or in the MR images of Patients 1 and 2, which were not acquired in 3D conditions.

Morphological analysis of MRI

MRI were first visually analysed according to a number of criteria (topography of the dysgenetic cortex around the sylvian fissure, cortical thickness, appearance of the cortical–subcortical junction, sulcal pattern, CSF spaces, white matter abnormalities), as proposed by Raybaud et al. (1996). An objective parameter reflecting the sylvian fissure depth was then determined for each spatially normalized, 1-mm voxel resolution, MR image. This was done on sagittal planes by measuring the x-coordinate of the parasagittal and centrifugal extremity of the sylvian fissure compared with control subjects (see text and Fig. 1).

Statistical parametric mapping of PET and MR images

MRI of 2-mm voxel resolution were segmented into four compartments (grey matter, white matter, cerebrospinal fluid and extra-cerebral tissues) using a maximum likelihood ‘Mixture Model’ clustering algorithm which has been validated (Ashburner and Friston, 1997). Only images of the grey matter compartment were further considered in the statistical analysis. PET and grey matter MRI were then smoothed at 12-mm full width at half maximum to increase
the signal to noise ratio. Effects were estimated according to the general linear model at each and every voxel (Friston et al., 1995b).

Subtractive studies were designed to compare each patient with the control group for both modalities of imaging (FDG-PET and MRI). The grey matter threshold was 0.5 for MR images and 0.8 for PET images. Among the control group of subjects aged 6–38 years that we used for FDG-PET analyses, we have shown a non-linear increase of adjusted glucose metabolism with age in several regions (thalamus, cingulate, basal ganglia and insula) (Van Bogaert et al., 1998b). To take into account these age-related metabolic changes, the absolute and squared values of age were considered as confounding covariates. Effects of global activity were removed using proportional scaling. An unpaired t test based on two contrasts was used to test the hypotheses for focal effects. The resulting SPM{t} was transformed into a normal distribution, SPM{Z}. The voxel Z-value and the spatial extent (k) were thresholded at uncorrected P-values of 0.001 and 0.5, respectively. To provide correction for multiple comparisons, SPM{Z} was analysed using two levels of statistical inference: (i) at the voxel level (Z-value), i.e. the probability that the observed voxel Z-value, or a higher value, could have occurred by chance in the volume analysed; and (ii) at the cluster level (k, Z), i.e. the probability of getting a cluster of the size observed, or larger, in the volume analysed (Friston et al., 1996). The threshold chosen for both levels of statistical inference was \( P < 0.05 \).

To take advantage of the statistical power of group comparison, patients were then considered together as a group and compared with the control group. Statistical inference was tested as above.

Coregistration with MRI
SPMs obtained from either FDG-PET or MRI analyses were coregistered with the spatially normalized MR images of each subject.

PET scans of Patients 1 and 5, for which spatial normalization was not achieved, were coregistered with their MRI-T1 sequences. This between-modality registration was performed by first segmenting MR images and then recombinig the partitions such that they emulate PET images (Ashburner and Friston, 1997). A visual analysis was performed in these patients by confrontation of coregistered PET and MR images.

Results
Table 1 summarizes the clinical, EEG and MRI investigations of the patients.

Aetiopathogenic factors
Patient 1, previously reported by Van Bogaert et al. (1996), and Patient 5 both issued from a monochorial twin pregnancy with occurrence of a twin–twin transfusion syndrome and death of the co-twin at mid-gestation. A genetic cause is probable in Patients 8 and 10 who were siblings from non-consanguinous parents originating from Macedonia. Familial and personal histories were unremarkable in the other patients.

Clinical and EEG features
It is noteworthy that signs of pseudobulbar palsy were observed in only eight out of 10 patients; indeed, Patients 8 and 10 were not dysarthric, did not show facial diplegia with automatic voluntary dissociation, and were able to move their tongues without limitation.

Interictal focal or multifocal epileptiform discharges were found on EEG in seven patients (see Fig. 2) but only five of them were epileptic. In Patient 10, a 32-year-old woman, seizures were mainly clusters of epileptic spasms resembling infantile spasms, as described by Gobbi et al. (1996) in children or adolescents with cortical dysgenes (Fig. 3).

Analysis of MRI data
A morphological analysis was first performed with particular attention to the sylvian fissures. According to the x-coordinate of the sylvian fissure at its parasagittal and centrifugal extremity, patients had either bilateral (seven cases) or unilateral (three cases) perisylvian pathology, this coordinate being more mesial in patients than in control subjects (\( P < 0.05 \) in patients with normalized MRI). However, in one unilaterally affected patient for this criterion, the contralateral sylvian fissure looked abnormal, being largely opened in conjunction with upper temporal atrophy. Ploughing of the abnormal sylvian fissure into the white matter varied from
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Fig. 2 Patient 4. EEG shows epileptiform abnormalities which are mainly localized in the left rolandic region. A second independent focus of spikes is present in the right rolandic region. Secondary generalized spike-waves occasionally occur.

one patient to another and was associated with ectopia of the surrounding dysgenetic cortex (see Figs 4 and 5); Patient 9 even had true closed-lip schizencephaly, with polymicrogyria extending from the subarachnoid spaces to the lateral ventricles. The abnormal perisylvian cortex appeared festooned, with irregular transition into the white matter, and thickened (5–8 mm) in eight patients but had normal thickness and shape in the other two patients (see Fig. 1). The polymicrogyric-like cortex frequently extended beyond the perisylvian region in the frontal, parietal or temporal cortices (see Fig. 4). Two patients showed considerable ventricular enlargement related to atrophy of the posterior white matter. The malformation was never strictly symmetrical, and focal enlargement of subarachnoid spaces beside the abnormal sylvian fissure was always observed.

Results of the voxel-based analysis using SPM of the grey matter images by comparison with a control group, performed in seven patients, are summarized in Table 2 and illustrated in Figs 4 and 5. The term ‘hyperintensity’ was used to characterize regions with voxel $Z$-values statistically higher in patients than in control subjects; ‘hypointensity’ referred to regions with voxel $Z$-values statistically lower in patients than in control subjects. This method was powerful enough to detect ectopic cortex, which appeared as a subcortical area of increased intensity. Bilateral pathology was detected using this method in a patient considered to be affected by unilateral perisylvian dysgenesis after morphological analysis of MRI (Fig. 4). The polymicrogyric-like cortex did not show decreased intensity in any patients. On the other hand, areas of decreased intensity were identified in cortical regions appearing either normal (two cases) or atrophic (one case).

Matching of FDG-PET and MRI data

In Patients 1 and 5, a visual analysis of the PET images was performed after coregistration with MRI, showing either bilateral high metabolic activity in the abnormal dysgenetic cortex or a heterogeneous pattern, with areas of preserved and areas of decreased metabolism within the polymicrogyric cortex.

In the other eight patients, the distribution of glucose metabolic activity adjusted to the global cerebral activity was compared with a control group using SPM (Table 2). Areas of hypometabolism were identified in four patients. One of them had extensive left frontal, perisylvian and parietal hypometabolism which concerned the polymicrogyric-like cortex (Fig. 4). In the other three patients, these hypometabolic areas concerned frontal, parietal or temporal cortical regions which had a normal appearance as well as normal signal intensity on MRI (see Fig. 5). In six patients, SPM identified subcortical perisylvian areas of increased glucose metabolism with regard to the white matter activity at this location in the control group. These areas of ectopic grey matter activity were in close relationship with areas of increased intensity detected by SPM analyses of MR images (see Fig. 4). Two patients did not show any abnormal regional distribution of cerebral glucose metabolism.

Group analyses of FDG-PET and MRI data using SPM

FDG-PET and grey matter MR images of the patients were analysed as a group by comparison with the control groups. Bilateral subcortical perisylvian hypermetabolism and hyperintensity were found using this strategy. Whereas the analysis searching for areas of decreased intensity did not reveal any significant areas when considering patients as a group, multifocal cortical areas of glucose hypometabolism were identified; the latter had already been identified by individual analyses of the patients except two symmetrical cortical areas localized in the frontal opercular regions (Fig. 6).

Discussion

We studied 10 neurological patients who had a MRI-based diagnosis of unilateral or bilateral perisylvian dysgenesis. In eight of them, radiological signs suggestive of perisylvian
polymicrogyria were obvious at visual analysis; abnormalities concerned the sylvian fissure (extension posteriorly and upwards towards the parietal lobe) as well as the perisylvian cortex (increased thickness and festooned transition into white matter). However, in two patients, in whom diagnosis was suspected on clinical grounds by the presence of severe developmental pseudobulbar palsy, the perisylvian cortex was normal in thickness and shape. Raybaud et al. (1996) have already pointed out that the thickness of polymicrogyric cortex may be within the normal range, in agreement with pathological observations. In these cases, radiological diagnosis essentially relies on evaluation of the sylvian fissure shape. For this reason, we defined an objective criterion, chosen to characterize the degree of depth of the sylvian fissure and based on its projection in the sagittal plane. This was possible due to the fact that MR images had been normalized into the same anatomical space, allowing comparison with normal control subjects. This method showed that all patients with normalized MRI had abnormal sylvian fissure, the abnormality being unilateral in three of them. Using other criteria of analysis (open operculum at visual analysis in one case and ectopic perisylvian cortex detected by SPM in the other one) contralateral perisylvian MR abnormalities were identified in two of these three
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Fig. 4 Patient 4. SPM of regions of decreased glucose metabolism (blue), increased glucose metabolism (green) and increased MR grey matter intensity (yellow) are coregistered with the normalized T1-weighted MRI. On visual inspection of the MRI, the left sylvian fissure extends deeply into the parietal lobe and is surrounded by a thick cortex. The left inferior, medial and precentral frontal gyri as well as the postcentral gyrus also show a polymicrogyric aspect. The right hemisphere appears normal. SPM identifies diffuse hypometabolism in the polymicrogyric-like cortex. Subcortical hyperintense and hypermetabolic areas correspond to ectopic cortex. Ectopia is found on both the left and right sides, supporting the clinical and EEG evidence (see Fig. 2) of bilateral pathology in this girl, with apparently unilateral malformation on visual inspection of the MRI.

Fig. 5 Patient 10. SPM of hypometabolic regions (blue) and increased grey matter MR intensity (yellow) are coregistered with the normalized T1-weighted MRI. Hyperintense regions are identified in the ectopic dysgenetic cortex. Right frontal and bilateral temporal hypometabolic regions are mapped in cortical regions with normal appearance and normal intensity on MRI.

patients, both of them having EEG or clinical signs of bilateral pathology. These analyses indicate that MR interpretation may benefit from the definition of objective criteria based on statistical treatment of the images, and they confirm previous reports of patients with an apparently unilateral perisylvian malformation showing clinical evidence of bilateral lesions (Sébire et al., 1996). We therefore conclude, following Raymond et al. (1995), that perisylvian dysgenesis appears on MRI as a broad spectrum of malformations, ranging from unilateral subtle gyral or sulcal abnormalities to bilateral clefts bordered by grossly abnormal polymicrogyric-like cortex (schizencephaly).

If pseudobulbar palsy with automatic voluntary dissociation probably implies bilateral opercular lesions (Weller, 1993), the inverse is not true. Indeed, one patient with bilateral malformations (illustrated in Fig. 5) had no signs of pseudobulbar palsy. Other authors reported similar observations (Lee et al., 1994; Gropman et al., 1997). Clearly the clinical manifestations of the congenital bilateral perisylvian syndrome are more heterogeneous than initially suspected by Kuzniecky et al. (1993).

In four out of 10 patients, we identified clinical features which helped to discern possible aetiopathogenic mechanisms involved in perisylvian dysgenesis. In two patients, it is likely that cerebral hypoperfusion occurred as a consequence of a twin–twin transfusion syndrome and death in utero of the co-twin, as previously discussed (Van Bogaert et al., 1996). Genetic factors are obviously suspected in our two affected siblings, who show a unique association of unilateral and bilateral perisylvian dysgenesis within the same family (Gillain et al., 1996). This observation together with other reports of familial perisylvian dysgenesis (Kuzniecky et al., 1993; Avanzini et al., 1995; Andermann and Andermann, 1996) and familial porencephaly (Sensi et al., 1990) provides evidence that these conditions, although usually related to prenatal acquired destructive events, may also be genetically determined. This is backed by the recent finding of a mutation of homeobox gene EMX2 in siblings with schizencephaly (Granata et al., 1997).

The PET investigation with FDG was performed in all patients and data were analysed in most of them using SPM,
Table 2 Abnormal areas revealed by SPM of FDG-PET and MRI

<table>
<thead>
<tr>
<th>Patient</th>
<th>FDG-PET</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypermetabolism</td>
<td>Hypometabolism</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>R and L subcortical perisylvian</td>
<td>L cortical parietal</td>
</tr>
<tr>
<td>4</td>
<td>R subcortical perisylvian</td>
<td>L cortical frontal, perisylvian and parietal</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>R cortical parietal</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>R subcortical perisylvian</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>R and L subcortical perisylvian</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>L subcortical perisylvian</td>
<td>R cortical frontal, R and L cortical temporal</td>
</tr>
<tr>
<td>Group</td>
<td>R and L subcortical perisylvian</td>
<td>R and L cortical anterior opercular, multifocal cortical area</td>
</tr>
</tbody>
</table>

A method allowing a statistical voxel-based analysis of neuroimaging data (Friston et al., 1995b). Our hypothesis that these patients with probable perisylvian polymicrogyria could have a common metabolic pattern was not verified by the individual analysis of the scans. Indeed, two different metabolic patterns were identified in cerebral cortex which showed a polymicrogyric aspect on MRI. The first one, found in eight patients, was a pattern of metabolic activity not significantly different from that in the normal grey matter. The second pattern, observed in two cases, was a heterogeneous pattern of hypometabolic areas and areas of preserved metabolism within the polymicrogyric-like regions. When the dysgenetic cortex was in an ectopic situation, grey matter activity was identified where white matter is found in normal subjects; this pattern has previously been reported in other FDG-PET studies of patients with perisylvian dysgenesis (Falconer et al., 1990; Lee et al., 1994). Comparison, using SPM, of FDG-PET or segmented grey matter MR images with those from a control group was useful in identifying this displaced grey matter as an area of hypermetabolism or hyperintensity.

Three patients showed hypometabolic areas in cortical regions which appeared normal on MRI. MR images were analysed using SPM to identify possible changes of signal intensity in these areas of decreased glucose metabolism, yielding negative results. It should be mentioned that SPM did not reveal any areas of decreased signal intensity in cortex with dysgenetic MR aspect, whereas such areas were identified in the absence of visible lesion in two cases. Dissociation between metabolic changes on PET and morphology and signal intensity on MRI is not unexpected. Indeed, although it has been stated that pixel signal intensity reflects grey matter density (Wright et al., 1995), there is no evidence that this relationship is linear. Furthermore,

![Fig. 6](image)

Fig. 6 Comparison of eight patients with the control group. SPM of regions of decreased metabolism (blue) are coregistered with a T₁-weighted MRI template. Multifocal areas of hypometabolism are identified. In the frontal opercular regions, the hypometabolic areas (arrows) were not identified in any individual analyses.

Macroscopic grey matter density may not reflect the density of functional neuronal circuitry. On the contrary, the biological correlates of glucose metabolism are well established; glucose
consumption reflects mainly synaptic activity (Kadecaro et al., 1985) so that it may be assumed that synaptic activity of this morphologically normal, but hypometabolic, cortex was decreased. This suggests the presence of microscopic lesions which, in these patients, are probably dysgenetic in nature. Richardson et al. (1996) also concluded that PET could be more sensitive than MRI in detecting cortical dysgenesis. These authors studied benzodiazepine receptors in epileptic patients with cortical dysgenesis and, using SPM, identified abnormal binding of $^{11}$C-flumazenil in cortical regions that had a normal appearance on MRI.

We found that perisylvian dysgenesis may present with either high or low glucose metabolism in different patients. An explanation for these variable findings could be that metabolic activity is influenced by the variable epileptogenicity of the dysgenetic cortex. Electroanatomicographic studies have shown that patients with refractory epilepsy associated with cortical dysplasia may present ictal or continuous epileptogenic discharges which are not always detected on scalp EEG (Palmini et al., 1995). However, it is improbable that epileptiform discharges played a significant role in the high glucose metabolic activity that we observed in the dysgenetic cortex of most of our patients because only a few of them had drug-resistant epilepsy. Another clue to the interpretation of the PET data may be the cytoarchitecture of the probable histopathological correlate of perisylvian dysgenesis, i.e. polymicrogyria. Correlation between the pathological type of cortical dysgenesis and the pattern of glucose metabolism has been principally established for cortical dysplasia, which is usually hypometabolic (Chugani et al., 1990; Lee et al., 1994). We found only one patient described in the literature with pathologically proven polymicrogyria which had been explored by PET with FDG. In this case, the cortical dysgenesis was hypometabolic (Khanna et al., 1994). The most typical polymicrogyric pattern is a four-layered cortex with a prominent upper dense cell layer in continuity with the outer layers of the surrounding normal cortex and a deep cell layer bordering the white matter (Friede, 1989; Barkovich et al., 1992). These two dense cell layers are separated by a sparse cell layer. The latter is probably related to a post-migratory ischaemic laminar necrosis (at 20–24 weeks gestation) and is not found in unlayered polymicrogyria, suggesting that this situation results from an injury during neuronal migration (at 13–16 weeks gestation) (Barth, 1987). We postulate that, depending on the importance and timing of the brain injury, the number of synaptic connections in the dense cell layers will vary so that a variable degree of hypometabolism will be found. This hypothesis is supported by our group analysis showing bilateral frontal opercular hypometabolism, which was not demonstrated by the individual analyses of the scans. Indeed, demonstration of hypometabolism in these perisylvian cortical areas which are precisely involved in the corticobasal type of pseudobulbar palsy with automatic voluntary dissociation (Weller, 1993) indicates that the decreased glucose consumption of the polymicrogyric cortex may not be intense enough to be detected in individual patients. Future activation studies may help to characterize functional capacities of dysgenetic cortex which is metabolically active at rest and of morphologically normal hypometabolic cortex.

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