Cortical Thickness Reduction of Normal Appearing Cortex in Patients with Polymicrogyria

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ABSTRACT

OBJECTIVE

To examine cortical thickness and volumetric changes in the cortex of patients with polymicrogyria, using an automated image analysis algorithm.

METHODS

Cortical thickness of patients with polymicrogyria was measured using magnetic resonance imaging (MRI) cortical surface-based analysis and compared with age- and sex-matched healthy subjects. We studied 3 patients with disorder of cortical development (DCD), classified as polymicrogyria, and 15 controls. Two experienced neuroradiologists performed a conventional visual assessment of the MRIs. The same data were analyzed using an automated algorithm for tissue segmentation and classification. Group and individual average maps of cortical thickness differences were produced by cortical surface-based statistical analysis.

RESULTS

Patients with polymicrogyria showed increased thickness of the cortex in the same areas identified as abnormal by radiologists. We also identified a reduction in the volume and thickness of cortex within additional areas of apparently normal cortex relative to controls.

CONCLUSIONS

Our findings indicate that there may be regions of reduced cortical thickness, which appear normal from radiological analysis, in the cortex of patients with polymicrogyria. This finding suggests that alterations in neuronal migration may have an impact in the cortical formation of the cortical areas that are visually normal. These areas are associated or occur concurrently with polymicrogyria.

Keywords: Epilepsy, FreeSurfer, volumentric MRI, cortical reduction in polymicrogyria.

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Search Terms: Volumetric MRI use in epilepsy, MRI, volumetric MRI, cortical reduction in polymicrogyria

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Introduction

Neuronal migration is a complex process occurring from the 7th week to the 3rd trimester of gestation, and requires normal structure and function of the glia (and cell microtubules). The direction of neuronal migration generally tends to follow a radial pattern, guided by specific proteins, in order to form the six-layered cortex. Neurons can also migrate in other directions, and often the final direction is parallel or at a tangent to the original migration pathway, usually taking place when the cells have already reached their destination. There are also a variety of mechanisms or agents that can influence this process and result in different types of disorders of cortical development (DCDs). One of the patterns found in DCD is a cortical disorganization characterized by an excessive number of small gyri and abnormal cortical lamination, defined as polymicrogyria.

There is a large literature in polymicrogyria[1] and awareness of the genetic mechanisms underlying morphological alterations in the cortical mantle,[2] as well as an improved understanding of the underlying neuronal migration patterns. Polymicrogyria has been associated with environmental factors and genetic alterations, especially when the changes are reported bilaterally. In addition to these transient neurodevelopmental factors, an interaction of ambient and genetic influence is also one of the plausible determinant factors in polymicrogyria phenotypes.[3-5]

There are a few genetic classification schemes and many radiological findings. Polymicrogyria is described as part of type I malformation, in association with extreme microcephaly, and is present in most of the type III malformations, where it may be associated with schizencephaly, polymicrogyria, and multiple congenital anomaly/mental retardation syndromes as: Adams–Oliver, aicardi, arima, oculocerebrocutaneous (Delleman), Galloway–Mowat syndromes, as well as microsyndrome and thanatophoric dysplasia.[6,7]

Newer technologies are also providing more information about the DCD pathophysiology.[8] However, little is known about the overall status of cortical organization since most of the studies have focused on the areas with noticeable cortical change, although polymicrogyria can be either focal or cover a large area of cortical mantle.[9-16]

We sought to investigate the whole brain in vivo by analyzing data from magnetic resonance images of patients with a

subtype of DCD in order to reduce variability and provide a more reproducible design. Our aim in this paper is to investigate polymicrogyria using cortical surface-based analysis of the whole cortical mantle (including abnormal and apparently uninvolved cortex), obtained from volumetric magnetic resonance imaging (MRI) data sets from patients compared with normal volunteers.

Methods

We studied 3 patients with polymicrogyria, who had been treated in the ambulatory of epilepsy at Hospital das Clínicas da Universidade de São Paulo (P1: age 18 years, male; P2: age 18 years, female; and P3: 13 years, female). Clinical symptoms (Table 3; row 2) included delayed neuropsychological development and refractory epilepsy (P1, P2, and P3). P3 also had shown signs of brain steam atrophy at the right side. The inclusion criteria for the polymicrogyria patients were: image MRI diagnosis made by 2 independent radiologists, refractory epilepsy, and age between 10 and 30 years. The exclusion criteria for patients with polymicrogyria were: previous neurosurgery, dehydration, use of corticosteroids in the last 30 days, and history of *status epilepticus*. All these subjects included in the study had their medical records evaluated by one of the authors (CCL). The comparison group consisted of 15 healthy subjects (mean age 26 years, standard deviation 4 years; range 15-31 years), who were recruited from the same regional population. Exclusion criteria for our healthy comparison group were: any chronic medical disorder (eg, depression, heart failure, stroke, etc), any neurological disorder, and convulsive episodes or a family history of epilepsy. The interviews were conducted personally. The ethics committee of the local university hospital approved the study protocol and all subjects provided written informed consent.

Magnetic Resonance Imaging

The study was conducted using a 1.5 T General Electric Signa^{TM} MRI Scanner (GE Healthcare, Milwaukee, WI), with gradient of 33 mT/m, using quadrature head coil and magnetic field isocenter positioned in the medial edge. The images were acquired using a 3-dimensional FSPGR pulse sequence in coronal plane, repetition time (TR), 20 ms; echo time (TE), 2 ms; slice thickness, 1.50 mm (zero filled .8 mm); flip angle, 25°; field of view, 20 × 18 cm; BW, 10.2 kHz; matrix dimension, 256 × 192; excitation count, 1; number of images, 236; time of acquisition, 5.46 minutes.

For each subject the MRI data set acquired was converted to FreeSurfer data format (http://surfer.nmr.mgh.harvard.edu).

A reliable cortical thickness method describe in detail in Dale et al[17] and Fischl et al[18,19] was used to calculate the thickness in a tessellated model of the cortical surface. This technique has tested in patient population and showed plausible results.[20] In summary, the technique is composed by several segmentation, normalization, and classification steps. The white matter is labeled using the voxel intensity and geometric continuity. The gray/white matter interface is tessellated and has topological defects corrected. This interface is the seed to a model of an accurate representation of the pial surface.[21] For each MRI data set the cortical thickness is calculated using the minimum distance between the interface surface and pial surface. This calculation provides submillimeter resolution on the measure of cortical thickness.[22] These measures were associated with the inflated surface mesh of each data set, with one cortical thickness value per vertices. In order to have a group map of the cortical thickness surface, an intersubject average using an spherical coordinate system are performed.[19] Also automatic cortical parcelation was conducted in order to have information related to the average thickness and volume data for different cortical regions.[23] We used an implementation of the general linear model over the surface values in the group statistical analysis.[20] In this test, each polymicrogyria subject was compared with the control group. We chose not to group all the polymicrogyria patients because of the distinct nature of their individual lesions and planed to determine individual neuronal migration pattern compared with a normal population.

Results

We analyzed the cortical thickness of each patient with polymicrogyria compared with the control group using the method described by Fischl and Dale.[22] The result of one subject is displayed in Figure 1. In the region where polymicrogyria was evident using the classical radiological approach (Table 1), there was a significant thickening of the cortex compared with the control group (point A in Fig 1). The areas with increased cortical thickness are listed in Table 2A.

On the other hand, in the areas where there was no apparent cortical malformation on radiological examination, we observed significant and clustered regions of cortical "thinning" (point B in Fig 1). The areas with reduction of cortical thickness are listed in Table 2B.

To check if the cortical thickness variation is related to atrophy of some other region, we calculated the volume of the basal ganglia (palidum, putamen, caudate), thalamus, ventricles, total gray matter, and total white matter in all subjects. The results in Table 3 show that the values were within the normal range of our control volunteers.

We have also identified other regions of significant change in cortical thickness, but these areas were scattered along the surface and did not form a cluster. The comparison of three randomly selected normal subjects' surface cortical thickness with the control group ($P < .01$) illustrate this variable pattern (Fig 2A), different from the result seen when we compared the subjects with Polymicrogyria (Fig 2B).

Discussion

One unanswered question relates to the fate of the remaining, apparently unaffected, neurons in polymicrogyria. This could be addressed using microstructural neuropathological methods, which are time consuming and complex to implement. In the past, the focus of neuropathological investigations has been on the macroscopically altered regions, and it was not a common practice to analyze the remainder of the cortical mantle. Examining the remaining cortex is particularly important since treatment of epilepsy in these disorders may include resection of polymicrogyric cortex, although evidence suggests that the epileptic origin in these cases may involve an extensive

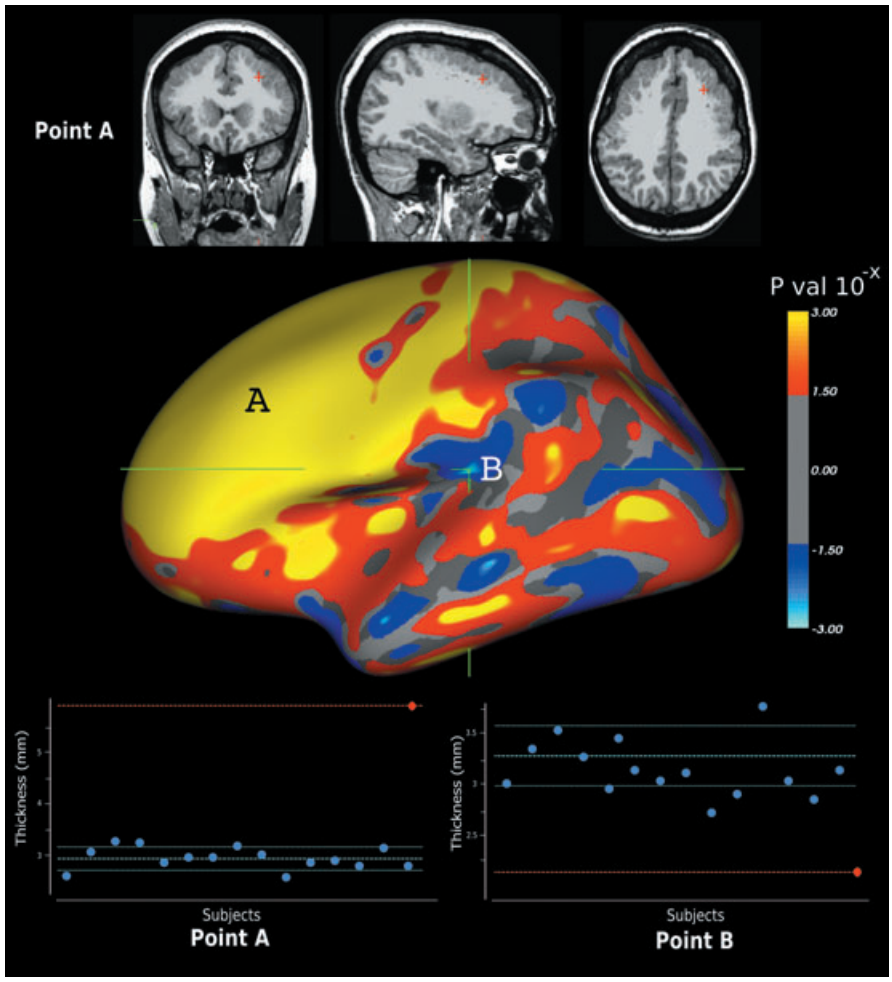

Fig 1. First row: coronal, axial, and saggital views of the original MRI SPGR images. Point A is identified by a red "+" sign. Second row: an inflated surface representation of cortical *P* value representing thickness (red and yellow areas are increased cortical thickness, light and dark blue are areas of reduced thickness of patient P1 compared with the control group). Third row: graphical representation of the values at point A (increased cortical thickness) and point B (reduced cortical thickness) of patient P1 (red dots) compared with the control groups (each subject blue dot).

network.[24] Furthermore, the polymicrogyric cortex may itself also be necessary for normal behavior, precluding the resection. There is evidence of functionality in these polymicrogyric regions from different techniques, including functional magnetic resonance imaging in visual,[25] language, and sensorimotor[26] polymicrogyric cortices.

The hypothesis that the remaining cortical gray matter from patients with polymicrogyric areas is abnormal, is supported by our findings. Three possible scenarios arise in this context: one would imply a relatively normal developmental trajectory in the apparently unaffected regions, so that the cortical thickness is expected to be preserved; the second option is that the remaining neurons are abnormal due to loss of connectivity or exposure to constant aggression from epilepsy; or third, these regions are actually affected, and the neurons are not normally formed. In the latter case, if the neuronal population would be reduced, as reflected in its volumetric representation. This could represent a secondary consequence of a neuronal migration to the affected polymicrogyric cortex, which contributes to the increase the cortical thickness in those areas. Neuronal migration in the tangential direction has been described by Rakic.[10,12] In the altered migration processes, the neurons do not follow the normal pattern of centrifugal pathway dictated by the radial fibers.[27] Instead, the neurons do not form the cortical layers in order of migration, ie, layer 6 before layer 5, and so on. The result is a mixture of cell location and specificity, and this may result in foci of neuronal discharges, generating the epileptic symptoms.[27]

There is no evidence that this abnormal migration is solely responsible for the augmentation of cortical thickness. Indeed, the number of neurons in those regions seems to be increased (at least neuronal density). What is found in our results is consistent with either two of the last possibilities state above.

In fact, nonradial cell migration differs from radial cell migration in the mechanisms of cell guidance as well, as the axons seem to be the counterpart of the radial glia in tangential migration process.[28] Most GABAergic interneuron, if not all, are believed to reach their final cortical location via tangential migration.[28,29] It is possible that tangential migration of the neurons from the parietal regions may be one of the mechanisms

Table 1. Radiological Findings in Visual Analysis

	P1	P2	P3
Radiologist 1	PMG bilateral (F)	PMG unilateral R (F,P)	PMG unilateral R (F,P)
Radiologist 2	PMG bilateral (F,P)	PMG unilateral R (F,T,P)	PMG unilateral R (F,P,T)

Report of visual analysis of two independent radiologists (Radiologist 1, Radiologist 2) of the three polymicrogyric patients (P1, P2, P3). PMG = polymicrogyria; F - frontal cortex; P = parietal cortex; T = temporal cortex; R = right; L = left.

Table 2. (A) Example of Areas where Cortical Thickness are "Increased" in Polymicrogyric Patients; (B) Example of Areas where Cortical Thickness are "Reduced" in Polymicrogyric Patients

	Cortical Thickness at the Sampled Point			
Anatomic Region (Talairach Coord)	**Control (Avg ± Std)**	**P1**	**P2**	**P3**
(A) Increased Cortical Thickness				
Left frontal pole (−13.9, 65.6, 19.5)	2.93 mm ± .21	5.93 mm		
Right middle frontal gyrus (26.9, 35.4, 18.0)	2.72mm ± .23		5.01 mm	
Right frontal lobe (28.5, 37.7, 10.9)	2.58mm ± .25			5.11 mm
(B) Reduced Cortical Thickness				
Left parietal lobe (−37.5, −37.5, 20.7)	3.42mm ± .33	2.03 mm		
Right parietal lobe (39.3, −32.0, 36.3)	3.56mm ± .21		2.37 mm	
Right superior temporal gyrus (38.9, −29.0, 14.9)	3.24mm ± .30			1.50 mm

Talairach Coord = talairach coordinates of sampled points in (x, y, z) of the representative regions; Avg = average; Std = standard deviation.
P1, P2, and P3 are patients with polymicrogyria.

to explain, at least in part, the altered cortical mantle in the polymicrogyric areas.[30]

Furthermore, our findings have highlighted the diagnostic potential of cortical surface-based analysis. Some of the thickened cortical regions may be overlooked because the observer is not able to distinguish the infolding and normal variations in cortical thickness in the 2-dimensional sections, even if using multiplanar reformations. On the other hand, there is no atlas and even no training methods to specifically expose the radiologist to cortical thickness variation in the healthy population across the whole cortex. This method is one of the computer-aided diagnostic tools available to help medical decision, when complex information has to be taken into account to improve health care.

Several articles have been published using the cortical surface-based analysis, including comparison with volume-based morphometry, showing its superior ability to match histological findings.[31] There are many examples with the same technique used in our study, covering diseases where the cortical thinning or thickening is altered in specific or generalized

Table 3. Clinical Data and Volumetric Measures of the Patients' Brains

	Patient 1	Patient 2	Patient 3	Healthy Subjects (mean ± std*)
Clinical Features	Mental Retardation Epilepsy	Mental Retardation Epilepsy	Mental Retardation Epilepsy, Brain stem atrophy at right side	
Caudate (mm^3)	7569	7915	7258	7939 ± 473
Putamen (mm^3)	11251	12019	12134	10897 ± 549
Palidum (mm^3)	3814	4169	3928	3893 ± 224
Thalamus (mm^3)	12448	13908	16820	16570 ± 714
Gray Matter (mm^3)	487568	458291	576558	558081 ± 23014
White Matter (mm^3)	459147	447590	424908	493645 ± 28564
Lateral Ventricles (mm^3)	16109	18052	8634	13792 ± 3108
3rd Ventricle (mm^3)	935	1482	662	908 ± 267
4th Ventricle (mm^3)	2083	2576	1272	1910 ± 464

*std = standard deviation (volumetric data from the control group for comparison).

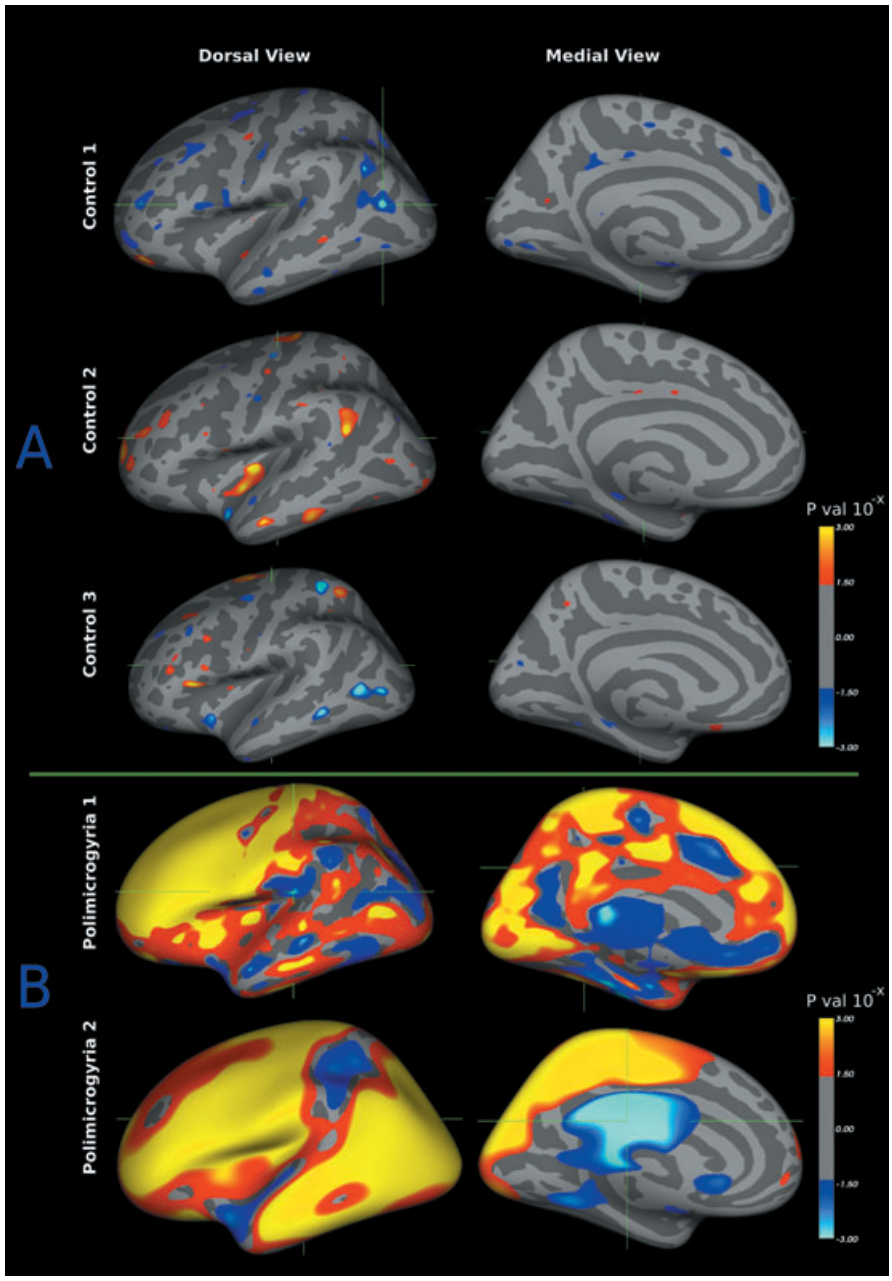

Fig 2. (A) An inflated surface representation of cortical *P* value representing thickness (red and yellow areas are increased cortical thickness, light and dark blue are areas of reduced thickness of three randomly selected controls compared to the whole control group). (B) Patients P1 and P2 compared with the control group, using the same notation.

brain areas, findings that are not easily assessed by visual inspection. Kuperberg et al[20] have shown that patients with chronic schizophrenia have widespread cortical thinning, especially in prefrontal and temporal areas. In a similar fashion, patients with multiple sclerosis have focal thinning in frontal and temporal areas, in addition to the diffuse cortical thinning.[32] Patients with dementia have also been investigated by cortical surface-based analysis. Dickerson et al[33] were able to distinguish the effect of normal aging and dementia in the thinning of medial temporal lobe, using the software implementation used in our analysis.

A sophisticated cortical morphometry technique, applied to the whole brain, also poses a few points. There is a debate about what would be the best approach to detect the number of neurons: mean cortical thickness or gray matter volume. Probably, the number of neurons is better correlated to volume of gray matter than with average thickness. However, there are some factors known to change the cortical volume without altering the number of neurons (dehydration, degree of neuronal arborization, intercellular space components, etc). In visual cortex, the proportion of neurons to glial cells is 2.04, meaning that roughly one third of the cellularity is due to other cell type, and

there are other volume occupying microstructures, such as water, myelin, etc.[34] Thus, the measures of cortical thickness or volume are not direct measures of the number of neurons. On the other hand, the fact that we detected a reduction in a specific area of neocortex is expected to be found; this is not a direct evidence of a disturbance in neuronal migration process, since other factors may interfere with cortical thickness. Nevertheless, if the neuronal population were reduced, one would expect a corresponding reduction in thickness and volume of gray matter. It is interesting to mention that other authors have found reduction in cortical volume at remote sites of patients with cortical dysplasia but did not provid an extensive investigation on those.[35] Techniques of neuronal labeling may help to clarify this possibility and help to further verify the nature of our findings.[28]

However, it is still to be determined if the method used here is robust under the case of patients with abnormal cortical formation. Although our patients did not have normal-appearing cortex, we have not used a straight registration to an atlas, as in traditional group mapping approaches, since this process is unlikely to produce correct results due to altered gyral pattern. FreeSurfer implementation of cortical surface-based analysis is distinct from other surface-based algorithms and conventional volume based morphometry with atlas mapping. Visual post-inspection and correction of segmentation have also provided the means for high degree of confidence on the measured values. The results presented in this paper could have valuable additional information if any of the polymicrogyria patients had undergone a resection neurosurgery; however, in our sample we do not have indications for this procedure.

On the other hand, cortical surface-based analysis calibration in humans poses a challenge. Although the precision of the method could be verified in post-mortem studies (providing histological measurements of cortical volume and thickness), tissue fixation bias could hamper this comparison. New methods are required to verify unambiguously the parameters obtained from cortical surface-based analysis.

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