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A framework for in-vivo quantification of regional brain folding in premature neonates

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1 Introduction

The percent of infants born preterm, or at less than 37 completed weeks of gestation, has increased significantly in the last two decades. A recent report [Hamilton et al., 2005] indicated that almost one in every eight births in the USA is preterm. There is growing evidence that premature birth can result in structural and functional alterations of the brain, which are related to adverse neurodevelopmental outcome later in life [Hüppi et al., 1996, Inder et al., 2005]. Some of the challenges that preterm infants face range from spastic motor deficits (cerebral palsy) [Volpe, 1998], impaired academic achievement [Hack et al., 2002, Cooke et al., 2004, Cooke, 2005], and behavioral disorders [Inder et al., 2003, Luciana, 2003]. However, the biological determinants of the cerebral abnormalities that underlie these common and serious developmental disabilities are not entirely understood [Inder et al., 2005]. The wider availability of clinical in vivo magnetic resonance imaging of neonatal brain anatomy, provided by systems which make use of an MRI compatible incubator, creates a new opportunity to quantify brain development.

We are particularly interested in the study of the degree of convolution of the brain cortex, or gyrification, in preterm infants. The process of gyrification is partially dependent on increased cortical volume and thickness and it proceeds in a spatial and temporal ordered sequence. It has been identified as a promising structural marker of neurodevelopment [Welker, 1990, Armstrong et al., 1995, van der Knaap et al., 1996] and can be derived from MRI data. Some of the changes in brain cortex at various stages is as follows. By mid-gestation (20 weeks) the brain is completed but is still very simple, primary convolutions begin to develop. Secondary sulci appear around the 24th week. At 28 weeks several elements are fully demarcated such as the calcarine fissure and superior temporal sulcus. Tertiary sulci appear between the 28th and the 37th week. The development of the pre- and post- central sulci is completed by 31 weeks and that of the central sulcus by 35 weeks [Raybaud et al., 2003, Encha-Razavi and Sonigo, 2003]. Regional alterations in gyrification may reflect the timing of injury in the developing brain and may have functional correlations. It is still not known how gyrification patterns change over time in the preterm brain [Kesler et al., 2006]. The long term goal of our research is to develop a methodology for in-vivo measurement of brain morphology in clinically

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acquired neonatal MR image data to be able to study normal gyrification and departures from it. At the heart of the methodology are mathematical measures that will allow a meaningful quantification of folding in whole brains and subregions. Several measures have been developed to quantify brain surface folding [Zilles et al., 1988, Van Essen and Drury, 1997, Magnotta et al., 1999, Ayaji-Obe et al., 2000, Batchelor et al., 2002], but an important limitation is that most of them are heavily dependent on the size of the surface being examined. Since brain surface area increases dramatically with brain development, previous measures cannot probe whether cortical folding is following a normal pattern, independent of size. Additionally these cannot be calculated on functional sub-regions of the cortex which may span different surface areas in different individuals.

The specific aim of this work is to develop a framework that will allow a meaningful examination of folding in healthy neonatal premature infants over a wide range of development, and within specific subregions of the cortex. Its foundation are new 3D global folding measures and two new approaches to area normalization of previously defined measures, both of which address the requirement of area-independence. The measures were tested on surfaces extracted from *in-vivo* MR brain scans from twelve premature infants with ages from 28–37 weeks to study the relationship between folding and age. The folding of whole brains, as well as their left and right hemispheres, was studied. There are three aspects of our work that are novel: 1) the proposed new measures and the two types of normalization for previously defined measures, which effectively enable the regional quantification of 3D cortical convolution; 2) extensive 3D analysis of gyrification on the interface between gray matter and white matter, in addition to the classically used interface between cerebrospinal fluid and gray matter; 3) quantification of gyrification from *in-vivo* scans of premature neonates covering an age range (28–37 weeks) of dramatic structural change. The developed framework has the potential of becoming a meaningful tool to examine brain gyrification in other contexts.

This paper is organized as follows. In Section 2, we describe previously defined measures that quantify the degree of cortical convolution and introduce the new 3D global folding measures. Details of the proposed framework and its implementation are also included in that section. Quantitative results of the application of new and previously defined measures to extracted surfaces from fifteen brains are presented in Section 3 and discussed in Section 4. Finally, in Section 5, we conclude our work. Part of the research reported in this paper has appeared in the conference papers [Rodriguez-Carranza et al., 2006c,a,b, 2007].

2 Methods

This section describes in detail previously defined measures that quantify folding, including a geometry-based example that shows their limitations, and then introduces new approaches to derive area-independent measures to study brain folding on 3D MR image data. This study is performed on two brain surfaces: the interface between the cerebro-spinal fluid and gray matter (CSF/GM) and the interface between gray matter and white matter (GM/WM). The overall framework for folding quantification from MRI consists of four major steps. Firstly, CSF/GM and the GM/WM boundaries are semi-automatically segmented and replicated; second, each surface is parcelled into subregions of interest; third, local curvature is computed at each voxel on a selected iso-surface; fourth, on a desired sub-region of the brain, global measures of folding are calculated from the local curvature estimation and geometrical properties. The global measures were investigated on two sets of iso-surfaces with different size/folding relationships, extracted from both CSF/GM and GM/WM. To study the performance of the measures, gyrification was quantified on whole brains and on left and right hemispheres, and the results were comparatively evaluated to a 3D version of the Gyrification Index. Lastly, a preliminary analysis of the effect of segmentation variability on the folding measures is described.

2.1 Measures to quantify brain surface folding

2.1.1 Previous global measures—Currently, the most widely used methodologies in the clinical arena to quantify the degree of convolution of the developing brain rely on visual assessment. The outcome is a numerical gyrification development score. These scores aim to take into account depth and width of sulci, complexity of sulcation and gyration, amount of convolutions, and density of the sulci [van der Knaap et al., 1996, Battin et al., 1998]; some additionally include changes in white matter and gray matter intensity [McArdle et al., 1987, Childs et al., 2001]. Such scores, based on qualitative visual assessment may not be sensitive to subtle changes in folding, occurring before 30 weeks of gestational age [Battin et al., 1998]. In addition, they are derived from separate 2D slices and do not take advantage of 3D information. There is therefore a need for a more formal, quantitative and sensitive scheme for the quantification of cortical folding in premature neonates which would complement clinical visual assessment.

For several decades researchers in other fields have been interested in identifying 3D mathematical shape-dependent quantities which are related to the degree of cortical convolution. One of the original concerns was to be able to identify and quantify evolutionary changes in size and shape of cerebral cortex in mammals [Elias and Schwartz, 1969]. Early attempts in defining an index of folding were based on geometric properties such as the isomorphy shape factor ¹, $ISF = A^{3/2}/V$, based on area (A) and volume (V); it was recently used to quantify shape differences in animal and human fetal brains [Mayhew et al., 1996]. Gyrification Index (GI) [Zilles et al., 1988] is another 2D folding measure and is defined as the ratio of the length of the entire cortical or inner contour (i.e. it includes sections buried in sulci) to the sum of the lengths of an outer contour, which is a manually-delineated envelope that connects all superficially exposed parts of the inner contour (i.e. it excludes the surface buried in sulci). Figure 3 shows a pictorial depiction of the inner contour (in black) of a brain slice and its outer contour (in gray). Brains with larger degree of convolution yield larger values of GI . It was recently used to compare gyrification in preterm and full-term children [Kesler et al., 2006]. It has been widely applied to assess gyrification patterns in adults with different neurological disorders including schizophrenia [Kulynych et al., 1997, Vogeley et al., 2000, White et al., 2003, Sallet et al., 2003, Harris et al., 2004], temporal lobe epilepsy [Oyegbile et al., 2004], Williams syndrome [Schmitt et al., 2002], and dyslexia [Casanova et al., 2004].

Recent attempts to quantify folding make use of surface curvature. It is a natural choice since curvature has been recognized as a key shape descriptor. In very simple terms, curvature measures the amount by which a surface (curve) deviates from a plane (straight line) [Dodson]. A maximal and a minimal curvature k_1 and k_2 are defined at each point on a surface; they constitute the principal curvatures (see the Appendix for a detailed description and graphical examples). Derived from those principal curvatures are local shape measures [Koenderink and van Doorn, 1992, Van Essen and Maunsell, 1980] such as mean curvature $H = \frac{1}{2}(k_1 + k_2)$,

Gaussian curvature $K = k_1 k_2$, shape index $s = \frac{2}{\pi} \arctan \frac{k_1 + k_2}{k_1 - k_2}$, curvedness $c = (\frac{1}{2}(k_1^2 + k_2^2))^{1/2}$, and the difference between maximal and minimal curvatures $k_1 - k_2$. Curvature-based global measures of folding constitute a linear averaging, over the whole brain, of various forms of such local shape descriptors. Examples of previously defined global curvature-based measures of gyrification are folding index (FI) [Van Essen and Drury, 1997], the intrinsic curvature index (ICI) [Van Essen and Drury, 1997], L^2 norm of the mean curvature (MLN) [Batchelor et al., 2002], L^2 norm of Gaussian curvature (GLN) [Batchelor et al., 2002], average curvature [Magnotta et al., 1999], and the whole cortex convolution index (WCCI) [Ayaji-Obe et al., 2000]. A list of previously defined global 3D measures of folding that are of interest to us is

¹The terms roundness (Rn), surface complexity [Magnotta et al., 1999], and isoperimetric ratio [Batchelor et al., 2002] have also been used.

shown in Table 1. All expressions were normalized to yield the unit value for a sphere. The measures score larger values for more folded brains.

Limitations of previous measures: There are several desirable properties that an ideal mathematical measure of folding should satisfy in order to be of true practical use [Batchelor et al., 2002]. Two of them are: 1) a measure should be independent of the acquisition plane and 2) a measure should score the same for brains that differ in area but that have similar degree of cortical convolution. In other words, measures should be invariant to rigid-body transformations and independent of the absolute surface area of the region of analysis. *GI* is independent of the absolute sizes of the sections of the brain and it has been shown [Zilles et al., 1997] that the variation of the mean *GI* with respect to acquisition plane is small (at most 8% when computed on standard coronal and two oblique coronal sections at $\pm 45^\circ$).

Examination of the form of the current global measures in Table 1 reveals a critical dependence on surface area. This can be better illustrated with the following example on a simple geometrical shape, which uses *MLN* to quantify folding. Take a whole sphere of radius Ro , half a sphere of radius Ro , and a whole sphere of half that radius. The three objects have the same surface complexity, hence a measure of global folding should yield identical results. By definition, $H = 1/R$ at each point in a sphere. From the expression shown in Table 1, an averaging of H over the sphere surface is required to compute *MLN*. Substituting, the whole sphere with

radius Ro yields $MLN = \frac{1}{4\pi} \sum_A H^2 = \frac{1}{4\pi} \times 4\pi Ro^2 \times (1/Ro)^2 = 1$, and so does the whole sphere with

radius $Ro/2$: $MLN = \frac{1}{4\pi} \times \left(4\pi \frac{Ro}{2}\right)^2 \times (2/Ro)^2 = 1$. On the other hand, *MLN* for the half sphere of

radius Ro is half that value: $MLN = \frac{1}{4\pi} \times \frac{1}{2} 4\pi Ro^2 \times (1/Ro)^2 = \frac{1}{2}$. This demonstrates the dependence of the measure on the size of the surface of analysis. Normalizing *MLN* with the surface area does not alleviate the problem, because the resulting normalized measure is dependent on size. E.g. for a whole sphere of radius Ro ,

$$MLN_A = \frac{1}{A} \sum_A H^2 = \frac{1}{4\pi Ro^2} (4\pi Ro^2) (1/Ro)^2 = \frac{1}{Ro^2}.$$

2.1.2 New approach: Area-independent global measures—In this work we explore two new general approaches to derive area independent measures of folding. The first approach is to incorporate normalization factors into previous curvature based measures. The second approach is to derive new intrinsically normalized measures using ratios of local curvature measures and geometric properties.

New measures with normalization factor: We address the problem of area dependence of current measures with two new normalization factors. One is based on volume and area

$$T = 3V/A \quad (1)$$

and the other on average mean curvature

$$|\bar{H}| = \left| \frac{1}{A} \sum_A H \right| \quad (2)$$

They were derived by measuring surface complexity on simple geometrical shapes; in particular, the example of the three spheres used earlier. Spheres have the advantage of having closed-form expressions for local curvature. The new normalized curvature-based measures, which are shown in Table 2, are created by applying the normalization factors to the previously

defined measures of Table 1. The normalized expressions are identified with a subscript T and H . For the case of a sphere, and substituting the definition of volume, area, and H into the expressions, we have $T = Ro$ and $|H| = 1/Ro$. Substituting this in turn on the MLN expressions of Table 2, it can be verified that $MLN_T = 1$ and $MLN_H = 1$ for each of the three sphere cases. The result clearly denotes independence to the area of the region of analysis. Similar results are obtained for the rest of the normalized curvature-based measures. The assumption in this approach is that the area-independence property introduced by the normalization factors will hold also on complex shapes such as the brain. Note that $\overline{K}_T^+$ is equivalent to ICI_T .

New measures based on local shape descriptors: Previously defined global folding measures are based on local shape descriptors such as H , K , k_1 , and k_2 . In this work, we propose three new measures based on shape index, curvedness, and difference of principal curvatures, which are also local descriptors (see definition in Section 2.1.1). The expressions of the new global measures, called Global Shape Index (GS), Global Curvedness (GC), and Global difference of principal curvature (Δk), are shown in Table 2. The shape index descriptor is a ratio of curvatures, so GS required only a normalization with area. GC and Δk were created by applying the normalization factors T or $|H|$ to the global averaging of curvedness and Δk , respectively. The reference again was the set of three spheres, for which the three measures yielded a value of 1.

New ratio curvature-based measures: In contrast to normalization of previously defined measures, we also examine measures based on the ratios of curvatures in order to create measures which are intrinsically independent of surface area. Here we look at two ratios of curvatures. Firstly, the ratio

$$SH2SH_T = T \sum_A H^2 / \sum_A H \quad (3)$$

derived from the mean curvature H , and secondly the corresponding ratio derived from the Gaussian curvature K :

$$SK2SK_T = T \sqrt{\sum_A K^2 / \sum_A K} \quad (4)$$

These expressions are normalized with T , to satisfy the area-independence property. Again, the three sphere cases constituted the reference and it can be verified that $SH2SH_T = 1$ and $SK2SK_T = 1$ for each case.

The coefficient of variation of H , $CV(H) = \sigma(H)/\overline{H}$ was considered as another potential new curvature-based ratio measure, but it is essentially equivalent to MLN_H .

New ratio area-based measures: Another alternative is to use measures derived from the fraction of the surface area categorized as concave or convex. This can be mathematically characterized by looking at the relative portion of the surface which has negative mean curvature (H^-) or negative Gaussian curvature (K^-). Thus the degree of folding can be captured by the fraction of the area (AF) with negative curvatures:

$$AF_{H^-} = A_{H^-} / A \quad (5)$$

and

$$AF_{K-} = A_{K-} / A \quad (6)$$

For an undeveloped brain, these fractions are expected to be small, and would progressively increase as the concave folds (sulci) appear. This new measure is inherently independent of the area of the region of analysis because it is a proportion. The area fraction with positive curvature is equivalent to the area fraction with negative curvature.

Overview of new measures: The new area-independent measures are summarized in Table 2. All measures, except *GS*, yield larger values for brains that are more folded. *GS* lays in the range [0,1], with spheres scoring the maximum value, which means that more folded brains have low *GS* scores. For consistency, the graphs of the results will show 1-*GS*, so that increased folding is connected to an increase in the value of the measure. For the same reason, AF_{H-} and AF_{K-} will be shown in the graphs instead of AF_{H+} and AF_{K+} .

2.2 Neonatal imaging protocol—High resolution ($0.703 \times 0.703 \times [1.5 - 2.2]$ mm) 3D T1 weighted spoiled gradient-recalled (SPGR) images were acquired on premature infants using a 1.5T GE MRI scanner with an MRI compatible incubator. The gestational ages of the twelve healthy premature infants in this study ranged between 24–31 weeks. The postmenstrual ages (gestational age + postnatal age) at the time of acquisition were 28–37 weeks. A subsequent scan for three infants was performed, hence a total of 15 brains were available.

2.3 Framework for brain folding quantification

2.3.1 Image segmentation and preprocessing—The segmentation of the newborn brain MRI is significantly more challenging than the segmentation of the adult brain [Prastawa et al., 2005]. The myelination process [Barkovich, 2000], which occurs at different times for different brain regions, results in white matter appearing with many different intensity characteristics and in a reversal of white/gray matter contrast. This tissue contrast variation for both gray and white matter, together with motion artifacts, low contrast to noise ratio, and the relative low resolution of the scans with respect to the small anatomy, make automated segmentation of the brain surface a challenge. Important advances for automatic segmentation of the neonatal brain for MR have been published [Prastawa et al., 2005], but for this work we relied on accurate manual segmentation to explore the behavior of the measures with high quality surfaces which were created using the rview software package (<http://rview.colin-studholme.net/>). This software combines a powerful user interface with a set of manual and semi automated labeling algorithms. Using rview, an automatic intensity-based segmentation was followed by an interactive manual correction of outlines. The CSF/GM interface was segmented first. Contours were traced in the three orthogonal directions, and adjacent sections were viewed for additional information. Non-cerebral tissue, cerebellum and the brain stem were removed, and the ventricular space was filled. Subcortical gray matter was not identified. Partial volume averaging is particularly problematic in “tight” sulci, where two adjacent GM banks have little CSF between them. If the walls of two adjacent gyri appeared to be touching, the criteria to decide whether to separate them or not was that a CSF invagination had to exist between them and the in-vagination had to be visible in the three orthogonal views. The segmentation of the GM/WM interface proceeded using the segmented CSF/GM boundary as a starting point, from which again an initial automatic intensity-based segmentation was followed by interactive manual correction. No distinction was made between myelinated and unmyelinated white matter. Significant interactive editing, taking between 2–6 hours, was required to get accurate and topologically correct segmentations.

CSF/GM was segmented for fifteen brains and GM/WM for thirteen brains. All the segmentations were done by one rater. An example is shown in Figure 1 where the outline of the segmented GM/CSF and GM/WM is overlaid on the original image. The segmented images were then binarized: a value of 1000 was assigned to foreground (i.e. brain) voxels and 0 to background voxels. Prior to curvature and Gyrfication Index estimation, and to allow a smooth surface representation without loss of fine scale features, the binary data were super-sampled using voxel replication. Given the original resolution of the data, it was found that a replication of $2 \times 2 \times 4$ voxels prior to smoothing preserved folding detail and provided close to iso-tropic resolution.

2.3.2 Curvature-based computation of brain surface folding—The approach to curvature estimation used in this work is based on surface gradients from iso-surfaces, and was derived from that developed by [Rieger et al., 2004]. It avoids the need of a parametric model and it computes curvature directly on voxel intensities. The input consists of the supersampled binary volume and a mask with labels which identifies the brain partitions of interest (see Section 2.3.4); the output consists of the local curvatures k_1 and k_2 at each voxel, from which local shape measures (H , K , c , s , Δk) are calculated. A summary of the sequence of steps is as follows:

1. Computation of the image gradient $g = \nabla f(x, y, z)$ of the replicated binary volume
2. Computation of the gradient structure tensor (GST) defined as $T = g g^t$
3. Calculation of the eigenvectors v_1, v_2, v_3 of T and the mapping $M(v_1) = \frac{v_1 v_1^t}{\|v_1\|}$
4. At each surface voxel (see text below) with percentage occupancy greater than τ (see text below) located in a partition of interest (see Section 2.3.4):
 - a. Computation of the principal curvatures k_1 and k_2 : $|k_{1,2}| = \frac{1}{\sqrt{2}} \|\nabla_{v_{2,3}} M(v_1)\|_F$ (Fröbenius norm). The sign of k_1 and k_2 is determined from the Hessian matrix of the image and the eigenvectors v_2 and v_3 .
 - b. Computation of local shape measures, which are multiplied by the voxel's area factor (see Section 2.3.3).

Steps 1,2,3, and 4a were derived from [Rieger et al., 2004]. After local curvature estimation, the surface area, its enveloped volume, and the global folding measures from Table 2 are calculated. The four steps of the curvature estimation algorithm involve image smoothing or differentiation. For all images, the 3D filters used at the i th step had a full-width at half maximum (f_i) of: $f_1 = 2.1\text{mm}$, $f_2 = 1\text{mm}$, $f_3 = 2\text{mm}$, $f_4 = 1\text{mm}$. The rationale behind the choice of values was to create a smoothly sampled iso-surface representation that would yield continuous variations in curvature. Small variations in f_2 and f_4 did not affect the final results. f_1 was selected to correspond to approximately six times the in-plane sampling resolution (after voxel replication) of the manual tracing. The value of $f_2 = 1$ was chosen empirically based on experiments with binary synthetic spheres for which H and K approached the theoretical values at that value of f_2 . The actual value of the computed k_1 and k_2 is important, since measures based on them are compared across non-isotropic brains of various sizes. It has been established [Lindeberg, 1993] that numerical values of spatial derivatives computed from smoothed data can be expected to decrease with the increase of the standard deviation of the Gaussian. Therefore normalized Gaussian derivatives were used for our computations to obtain consistent values of the principal curvatures across brains. The normalized Gaussian derivatives, expressed as three separate convolutions with 1-dimensional kernels are given by

$$f_{x^i y^j z^k}(\mathbf{x}; \sigma) = \sigma_x^i \sigma_y^j \sigma_z^k \left\{ \frac{d^i}{dx^i} G(\mathbf{x}; \sigma_x) * \left\{ \frac{d^j}{dy^j} G(\mathbf{y}; \sigma_y) * \left\{ \frac{d^k}{dz^k} G(\mathbf{z}; \sigma_z) * f(\mathbf{x}) \right\} \right\} \right\} \quad (7)$$

where i, j, k are nonnegative integers satisfying $i + j + k = 1$ for first order derivatives and $i + j + k = 2$ for second order.

The input to the curvature estimation algorithm is the binary replicated segmented brain, for which foreground voxels have a value of 1000 and background voxels a value of 0. The raw effect of the convolution (step 1 of the algorithm) is that the voxels of the resulting volume have intensities between 0 and 1000. Voxels with intermediate intensities represent *partial occupancy by brain tissue*. After convolution, a voxel with value C is said to have tissue

occupancy of $\frac{C}{10}\%$. E.g. a voxel with value 100 is said to have tissue occupancy of 10%. A large value of C means that more of the voxel's neighbors, in the preconvolved image, were foreground voxels. This convolved image is then binarized to identify the surface on which curvature will be estimated. All voxels with value greater than a threshold τ are classified as foreground, and those with value less than or equal to τ are classified as background. For example, a threshold of $\tau=500$ determines that voxels with $C > 500$ (i.e. tissue occupancy larger than 50%) are considered foreground, and those with $C \leq 500$ (i.e. at most 50% tissue occupancy) belong to the background. Curvature is computed on all surface voxels of the thresholded object. An object voxel is a *surface voxel* if it is 6-connected to at least one background voxel.

2.3.3 Computation of surface area and volume—Counting the number of such surface voxels is the simplest approach to obtain a surface area estimate of a 3D object, but it results in a severe underestimation [Lindblad, 2005]. For this work we used the fast and convenient voxel-based approach developed by [Windreich et al., 2003] which is suited for highly convoluted surfaces such as the brain. Each surface voxel is classified based on the number of faces that are exposed to the background and their configuration, and a weight factor is assigned accordingly. Since the voxels are non-isotropic, we need to consider the voxel dimensions for the estimation of surface area in cm^2 . In [Windreich et al., 2003] the voxel is of unit value, and the area contributed by a voxel v is the weight factor ω : $A(v) = \omega(v)$. In this work, the area for the non-isotropic case is computed as $A(v) = A_{EF}(v) * \omega(v)$, where $A_{EF}(v)$ is the average area of the exposed faces of voxel v . It is computed as the sum of the area (in cm^2) of each of the exposed faces, divided by the number of exposed faces. Note that for the isotropic case with unit value, $A_{EF}=1$. The volume of CSF/GM, in cm^3 , was calculated as the sum of the total number of CSF/GM surface voxels and all the object voxels enveloped by it (including the ventricular space), multiplied by the voxel dimensions; similarly for the volume of GM/WM. For the consistent computation of global measures of folding, the local shape measures at each surface voxel were weighted by the corresponding estimated area $A(v)$ at that voxel. The correctness of the calculations was verified with simple isotropic and non-isotropic geometrical shapes.

2.3.4 Cortical Partitioning using Spatial normalization—In order to study regional changes in surface folding across different subjects, we need to be able to identify boundaries from the structural image data which consistently partition the brain surface in different subjects at different stages of development. In this initial work we have used a single reference anatomy which was manually partitioned into left and right hemispheres. A multi-resolution B-Spline based spatial normalization, adapted from that described in [Studholme et al., 2004b,a] and as used in [Cardenas et al., 2005], was then applied to estimate a spatial transformation mapping from this reference to each subject MRI being studied. This

transformation was then numerically inverted to allow the assignment of the nearest reference label to a given subject image voxel, which brought the voxelwise partitioning of the reference anatomy to the same space as the surface extracted from each infant. The partitioning was then used to constrain the voxelwise evaluation of the folding measures.

2.4 Performance analysis

2.4.1 Whole brain folding quantification—The 15 neonatal brains analyzed in this work is characterized by an increase of size and folding with age. An iso-surface at 50% tissue occupancy was extracted from the segmented CSF/GM and GM/WM of each of those 15 brains. This set of iso-surfaces, called the *proportional set*, embodies the natural change of size and folding with age. The relationship between age and folding was investigated using regression and for this work a linear model was used. The measures were evaluated based on their goodness-of-fit (R^2). To further test whether the new measures can truly probe folding independently of size, a second set of iso-surfaces was analyzed. The surfaces of this set were extracted from the segmented CSF/GM and GM/WM of the 28-week old brain at percentage tissue occupancy in the range 5–95% (in increments of 5%), which correspond to 19 iso-surfaces per tissue boundary. This synthetic set, called *inversely proportional set*, was characterized by an inverse variation of size and folding: smaller brains were more folded. A larger tissue occupancy produces a smaller brain with wider and deeper sulci, which translates to increased folding, as seen in Figure 2 and Figure 8. The relationship of folding with tissue occupancy for this set is expected to vary monotonically: the larger tissue occupancy (i.e. smaller brain), the more folded the brain.

2.4.2 Regional brain folding quantification: left and right hemispheres—The degree of gyrification was quantified on left and right hemispheres, and compared to the gyrification of the whole brain. Intuitively, the complexity of the whole brain is similar to the complexity of left or right hemispheres. A measure of complexity that is independent of the area of the region of analysis should be able to capture this fact. The purpose of these experiments was to study the dependence of measures on the area of the surface of analysis. Note that complexity asymmetry between left and right hemispheres was *not* the concern of this analysis. To quantify the difference in complexity between left hemisphere (l) and the whole brain (w), we computed the percentage folding difference as $\Delta M^{wl} = (M^w - M^l)/M^w$, where M represents a folding measure. A similar expression, ΔM^{wr} , is defined for the right (r) hemisphere. Quantification of folding with previously defined measures is expected to score half of the value on left hemisphere than for whole brain, which means values of ΔM^{wl} of around 0.5 (similarly for the right hemisphere and ΔM^{wr}). The new area-independent measures are expected to yield similar values for each hemisphere and the full-brain, with some differences in gyrification anticipated since left-right asymmetry exists in the developing brain [Chi et al., 1977]; this means values of ΔM^{wl} and ΔM^{wr} of around 0. Regional folding quantification was performed in the brains of both proportional and inversely proportional sets.

2.4.3 Comparative evaluation to 3D Gyrification Index—The analysis of the new folding measures would not be complete without comparison to the widely used Gyrification Index. As mentioned in Section 2.1.1, classical 2D Gyrification Index is a used measure to quantify brain convolutions computed as the ratio of the lengths of the inner and outer contours. An outer contour constitutes an envelope that effectively wraps the brain surface. This can be seen in Figure 3, which is an example similar to figure 1 in [Zilles et al., 1988]. The delineation of outer contours was not intended to be convex, only an extension of the inner cortical contour that would cover the brain concavities. Outer contours could be manually delineated, but that is a very time-consuming task. Equally important, independent manual delineations are bound to differ, specially for such a complex shape as the brain. How large those differences may be and to what extent they may affect GI has not been investigated. A deterministic approach is

to approximate the outer contour by the convex hull of the inner contour. But a full convex hull is not useful because it would represent an outer contour that is a poor anatomical reference and would not be useful to capture small changes in folding. An example of this can be seen in Figure 4, in the temporal lobe area of the case at 160 iterations (rightmost case). That envelope is not convex but it already shows the loss of anatomical detail. Therefore, we choose to use a convex hull algorithm to generate an envelope that covers the concavities of the input shape and preserves anatomical detail, and which will not be a convex hull. We refer to this shape as the *semi-convex hull*.

For this work Gyrification Index is computed as a 3D entity and, instead of a ratio of lengths, it is computed as a ratio of areas. The segmented CSF/GM and GM/WM constitute the inner surfaces. The semi-convex hull of those inner surfaces was calculated with the convex-hull algorithm proposed by [Borge-fors et al., 1994]. A description of the sequence of steps to compute the 3D convex hull is as follows. To create smooth surfaces, the segmented replicated binary image was convolved with a filter of the same size as the filter in step 1 of the curvature estimation algorithm. The iso-surface at 50% tissue occupancy was extracted from the convolved image, and this constituted the inner surface. To create the semi-convex hull a $5 \times 5 \times 5$ neighborhood was selected to extract local curvature and a limit on the number of iterations allowed to fill local concavities was empirically set to 20 for CSF/GM and 40 for GM/WM. The 3D *GI* was computed as the ratio between the *surface area* spanned by the inner surface to that of the outer surface, defined by the 3D semi-convex hull of the inner surface. The area of those surfaces was computed as described in Section 2.3.3. An example of the 3D semi-convex hull of CSF/GM and GM/WM iso-surfaces of a 35 week old infant at 50% tissue occupancy, at 10, 40, and 160 iterations, is shown in Figure 4. The view is coronal; the brain delimited by the CSF/GM or GM/WM interface is shown in black and the space covered by the semi-convex hull in gray. Note that at 10 iterations very few concavities of the GM/WM surface have been filled by the algorithm, while most have been filled for CSF/GM. At 160 iterations, the envelope for both CSF/GM and GM/WM has filled all concavities, but some anatomical detail has been lost.

2.44 Assessment of the effect of intra-ob server segmentation variability on the folding measures—We investigated the extent to which differences in segmentation affect the folding measures with an approach similar to the one in [Batchelor et al., 2002]. The GM/

WM surfaces of two infants with age difference of $3\frac{1}{3}$ weeks (one was 29.1 weeks and the other 32.4 weeks of age) were segmented four times by one rater. The time elapsed between segmentations varied between one week and five months. The four segmentations (σ) at each age (α) constitute a set. The maximum percentage intra-age variation,

$V^\alpha = \max_\sigma (M_\sigma^\alpha - \bar{M}^\alpha) / \bar{M}^\alpha$, for $\sigma = 1, 2, 3, 4$, $\alpha = 29.1, 32.4$, M =folding measure, and

$\bar{M}^\alpha = \frac{1}{4} \sum_{\sigma=1}^{\sigma=4} M_\sigma^\alpha$ was taken as an indication of the variability of a measure with respect to segmentation. The variability of a folding measure with respect to age was calculated as the percentage difference between the means of the two sets, $(\bar{M}^{32.4} - \bar{M}^{29.1}) / \bar{M}^{32.4}$. The comparison of the intra-age variation and the inter-age variation was taken as an indication of the relative importance of segmentation variability with respect to the variability due to age. Whole brains were used for this assessment.

To estimate how much segmentations differed within each set, we used the dice similarity coefficient, *DSC*, a metric of spatial overlap. It is defined as $DSC(A, B) = 2(AB)/(A + B)$, the ratio of the number of overlapping voxels from two objects, over the sum of the voxels from both objects. *DSC* lies in the range [0, 1], with *DSC* = 1 for total overlap and *DSC* = 0 for no overlap. Conceptually, it is a measure of agreement. For objects such as brains the resulting

DSC is very close to one, therefore it was suggested [Zou et al., 2004] to adopt a logit transformation to stretch the range of *DSC*. The domain of $\text{logit}(DSC)$ is $(-\infty, \infty)$. From the statistics literature, *DSC* values larger than 0.75 ($\text{logit}(0.75)=1.1$) are considered excellent agreement, which translates into an extended overlap between segmentations.

3 Results

We quantified folding on iso-surfaces from 15 MRI brain. Linear regression was used to analyze the relationship between age and folding, and measures were evaluated based on the goodness-of-fit. We show results for whole brains and a regional analysis of left and right hemispheres. Two sets of surfaces with different size/folding relationship were studied: the proportional set and the inversely proportional set. A comparative evaluation to 3D GI and a preliminary assessment of the effect of segmentation variability on the folding measures are also presented.

3.1 Whole brain folding quantification

Proportional set—An example of local mean curvature mapped on the 50% tissue occupancy iso-surface of GM/WM is shown in Figure 5 for three different premature brains. The sulci are depicted in dark tones of gray and the gyri in bright tones.² Plots of global folding measures against age for whole brains on both CSF/GM and GM/WM are shown in Figure 6 and the goodness-of-fit from the linear regression is shown in Table 3. All values $R^2 \geq 0.70$ are highlighted in boldface. *T*-normalized measures rated best for CSF/GM and the best measures (goodness-of-fit of at least 0.85) were FI_T , Δk_T , $\overline{H}_T^+$, $\overline{K}_T^-$, GC_T . The measures with largest goodness-of-fit for GM/WM were MLN_H , GC_H , GS , and AF_{H-} . No single measure rated equally well for both CSF/GM and GM/WM. The result for *MLN* is included in the table, as an example of previously defined measures.

The slope of the regression for the *H*-measures is positive for CSF/GM and GM/WM, which indicates that folding increases with age. But note that the slope of the regression for all the *T*-measures is positive for CSF/GM but negative for GM/WM. From Figure 7 one can see that it coincides with the sign of the slope of *T* itself. The slope of $T = 3V/A$ for CSF/GM is positive because the rate of change of volume with age was faster than that of surface area with age, as seen in Figure 7. The inverse occurs for GM/WM. This has to be taken into account when interpreting the results for GM/WM. The new interpretation ought to be that for GM/WM, the older, larger, more folded brain surfaces score smaller values for the *T*-measures.

Inversely proportional set—Figure 8 shows local mean curvature renderings on GM/WM iso-surfaces at 10%, 50%, 90% tissue occupancy for the 28-week old infant. Note that the larger the percentage tissue occupancy, the smaller the brains and the deeper and wider the sulci are, which makes the brains more folded. Plots of global measures against percent tissue occupancy are shown in Figure 9. Folding quantified with *H*-measures, *GS*, *AF*, and the previously defined measures (represented by *GLN*, *MLN*, and *Rn*) increased with tissue occupancy, as expected. But the slope of the *T*-measures was negative, which seems to be again heavily dependent on the slope of *T* (Figure 10). Therefore, again, one has to expect smaller values of the *T*-measures for more folded brains.

As seen in Figure 10, the surface area of CSF/GM varied in a non-monotonic fashion, which is explained by the progressive separation (Figure 2) of the left and right hemispheres of brains created at larger tissue occupancy thresholds. The increase in surface area due to this separation

²The color version of the image shows a richer range of curvature values; there was a loss of information with the mapping from color to gray scale.

is dominant over the relative decrease in area due to the diminished brain size at larger thresholds. The surface area for GM/WM decreases monotonically in the range 5%–95% because the reduction in brain volume predominates over the increase in area due to increased infolding.

3.2 Regional brain folding quantification: left and right hemispheres

Proportional set—Plots of percentage folding difference (for left hemisphere vs whole brain, and right hemisphere vs whole brain) against age for six measures are shown in Figure 11. For the new measures the percentage differences ΔM^{wl} and ΔM^{wr} across all ages are distributed around 0, which means that the magnitude of the measures for whole brain is very similar to the magnitude for the left and right hemispheres. In contrast, the percentage difference for previously defined measures -represented by MLN and shown in the last graph of the figure- is distributed around 0.5, which means that the value of previously defined measures on left or right hemisphere is about half the value as for whole brains. This demonstrates the dependence of previously defined measures on the area of the surface of analysis and is strong evidence that the new measures provide significant improvements. The goodness-of-fit for measures of folding on left and right hemisphere were similar to the scores for whole brain.

Inversely proportional set—As for the proportional set, ΔM^{wl} and ΔM^{wr} were also distributed around 0.5 for previously defined measures and around 0 for the new measures, and so the graphs are not shown.

3.3 Comparative evaluation to 3D Gyrfication Index

Proportional set—The semi-convex hull of the inner surface of each brain was created at various thresholds, which gave an estimation of 3D GI for each threshold. 3D GI was compared to the four curvature-based folding measures which yielded the best goodness-of-fit on CSF/GM and GM/WM (Table 3). For CSF/GM, the goodness-of-fit for 3D GI against age was 0.69, 0.58, 0.54, 0.58 at 10,20,40, and 160 iterations respectively; in contrast, the fit for the new curvature-based measures was greater and in the range [0.80,0.85]. For GM/WM, 3D GI had a goodness-of-fit of 0.91, 0.95, 0.96, 0.95 at 10,20,40, and 160 iterations, respectively; the fit for the new curvature-based measures were in the range [0.93,0.94]. Plots of 3D GI for CSF/GM at 20 iterations and for GM/WM at 40 iterations are shown in Figure 12. The area of the inner surface of CSF/GM and GM/WM and of their 3D semi-convex hull, from which 3D GI is computed, are shown in the same figure.

Inversely proportional set—Figure 13 shows that 3D GI increases non-monotonically as the CSF/GM surfaces become more folded (at larger threshold or tissue occupancy). It also shows a *decrease* for GM/WM surfaces. A similar trend was observed when GI was computed with a 2D semi-convex hull and contour lengths.

3.4 Assessment of the effect of intra-observer segmentation variability on the folding measures

Iso-surfaces from the four segmentations of the 29.1 and 32.4 week-old brain were extracted at 50% tissue occupancy and the measures that scored the best goodness-of-fit for GM/WM (Table 3) computed. A subset of the results of the influence of segmentation on the measures is given next as a triplet, where the first number is the maximum percentage variation at age 29.1, the second is the maximum percentage variation at age 32.4, and the third is the percentage mean difference between both ages. The results are: MLN_H (2.81%, 2.75%, 26.4%), GS (1.43%, 4.81%, 16.5%), and AF_{H-} (0.95%, 3.26%, 10.23%), GC_H (3.35%, 3.11%, 30.83%), GI (0.21%, 1.39%, 13.79%). The variation in a measure caused by different segmentations can be visually

assessed in the plots of folding against age shown in Figure 14. This are the plots from Figure 6 but the scores for the four segmentations of the two selected infants (29.1 and 32.4 weeks of age) are shown with an asterisk.

Figure 15 gives a visual example of how segmentation differences were distributed around the brain. At each age, one of the four segmentations was randomly selected as a reference, and sample slices of the difference volume of the overlay of the reference segmentation with each of the other three independent segmentations is shown. The leftmost triplet denotes a sample slice and the second triplet denotes another. The first row is for the 29.1 week-old infant and second for the 32.4 week-old infant. The black dots are the voxels present in the first segmentation of the pair but not in the other; the gray voxels represent the converse case. The smaller the amount of dots appearing in the figure, the larger the similarity between two segmentations. Note that the region of the hippocampus gave the largest differences in segmentation. The similarity among segmentations was rated using *DSC*. The segmentation overlap, as quantified by *DSC*, is a pairwise comparison. Since there were four segmentations per infant, there are six possible pairwise comparisons. The minimum and maximum logit (*DSC*) of the six possible comparisons were: 3.73 and 5.33 (*DSC* of 0.977 and 0.995) for the 29.1 week-old infant and 2.71 and 3.32 (*DSC* of 0.937 and 0.965) for the 32.4 week-old.

4 Discussion

An understanding of the cortical folding process in the development of premature infants may be important in explaining and predicting abnormal neurological outcome. The use of formal mathematical descriptions of the brain surface provides a more quantitative tool to study the folding process than is available with simple visual evaluation of MRI scans. The long term goal of our research is to create a model to track preterm *in vivo* neonatal brain cortical development that will help characterize normal gyrification and departures from it.

Quantification of brain folding

Through the regional folding analysis on left and right hemispheres we have shown that most previously proposed measures of cortical convolution [Van Essen and Drury, 1997, Batchelor et al., 2002] are dependent of the area of the surface on which they are calculated. To alleviate this problem we examined two approaches to area normalization of the measures and proposed new forms of measure, which satisfy the requirement of area-independence. These were evaluated on neonatal brain surfaces. The measures' ability to detect change in normal development was evaluated by computing the linear regression of each measure with age. Finding folding measures which are a simple function of age is an important part of the goal of modeling brain development. We will explore higher order models when more data is available. GM/WM folding tracked best with age and no single measure rated consistently well for both CSF/GM and GM/WM. Overall, recommended measures for CSF/GM are T-normalized measures (specifically ICI_T , $\overline{H}_T^+$, $\overline{K}_T^-$, and Δk_T); when studying GM/WM gyrification, the recommendation is to use the $\overline{H}$ -normalized measures (MLN_H and GC_H), Global Shape Index (GS) or the area fraction with H^- (AF_{H^-}). The new measures with normalization factors were derived from simple geometrical shapes; the assumption in our work is that the area-independence property of these new measures is also valid for objects of arbitrary shape. Some evidence that this assumption is reasonable comes from the fact that the new normalized measures and the ratio area-based measure AF_{H^-} , a measure inherently independent of the area of the region of analysis, were all related to age in a similar way.

The inversely proportional brain set was a group of iso-surfaces extracted from one of the neonatal brains and was characterized by large folding for smaller shapes. The purpose of this set was to probe the question of whether measures quantify folding and not merely change in

volume. The new measures consistently quantified brain folding in this set. Even though the iso-surfaces of this set do not correspond to anatomically meaningful layers of the brain, they were extracted from real images and therefore retain the natural intrinsic complexity of the brain.

An anatomical description would help the user to interpret the global measures of folding. Unfortunately, except the indexes based on the ratio of areas, it is not trivial to present such a description for the curvature-based measures, since they represent a single number (i.e. an average of local curvature over the whole brain). Figure 5 and Figure 8 show the map of the mean curvature on the brain and provide some intuition to the reader of what was being averaged.

Comparative evaluation to 3D Gyrification Index

We compared the ability of 3D *GI* to that of surface, curvature-based folding measures to detect change in normal development. Gyrification Index has not been previously compared with surface curvature-based folding measures on scans from *in-vivo* neonatal premature infants. From the results of this work it is evident that the relationship between age and folding, as measured by area-independent folding measures and 3D *GI*, followed similar trends. This strengthens the claim that the normalization factors and new forms of measure proposed in this work are valid measures of 3D folding. The results show that on CSF/GM surface curvature-based folding measures appear to track age considerably better than 3D *GI*. Since the sulci in CSF/GM are not as exposed as those in GM/WM, the difference in area between the inner and outer surface is small (Figure 12). Therefore, it appears that *GI* cannot capture changes in folding of CSF/GM with age as well as the curvature-based measures. In contrast, the relationship of folding and age on GM/WM surfaces had comparable goodness-of-fit for both curvature-based measures and 3D *GI*.

The results for the inversely proportional set showed that 3D *GI* for CSF/GM increased with folding, albeit the area of CSF/GM changed in a non-monotonic fashion (center plot in Figure 13). On the other hand, the results for GM/WM were intuitively unexpected: the 3D *GI* score was lower for more folded surfaces. In Figure 13 (rightmost plot) it can be seen even though both the GM/WM surface and its outer surface decrease with percentage occupancy, the slope of both will cause the plot produced by their ratio (by definition the 3D Gyrification Index) to have a negative slope; this is seen on the leftmost plot of the same figure. The results suggests that 3D *GI* was not able to capture the change in folding for GM/WM surfaces of the inversely proportional set. For this set, 3D *GI* seems to follow the trend of the change in area, which is a decrease in value for smaller, more folded brains. This is in contradiction with the results from the new measures, which all show consistent change in value with increased folding.

New measures are independent of the region of analysis

Three forms of evidence were provided that support the claim that previously defined measures are dependent on the area of the region of analysis, and that the new measures are independent: a) a formal demonstration with simple geometrical shapes and their closed-form expressions of *H* and *K*; b) the results of the empirical regional comparison of left hemisphere vs whole brain and right hemispheres vs whole brain; c) the results from the comparative evaluation to the 3D Gyrification Index, a measure known to be independent of the region of analysis.

Assessment of the effect of intra-observer segmentation variability on the folding measures

The variability of a measure with respect to segmentation was smaller than the variability with respect to age for GM/WM surfaces, in a 3-week interval. Of the measures tested, the variability with respect to segmentation was ten times smaller than the variability with respect to age for the 29.1-week old case, and also ten times smaller for the 32.4-week old case, except for 2

measures for which the difference was only 3 times. Those two measures, AF_{H-} and GS , might be more sensitive to the relatively coarse segmentation differences, shown in Figure 15. The overlay of segmentations is useful to see the extent of the segmentation errors and their distribution along the surface. The values of $DSC > 0.93$ for all pairwise comparisons was well into the range considered of excellent agreement ($DSC > 0.75$), which indicates that the degree of similarity among the four segmentations per brain was large. DSC results indicate that the segmentations of younger, less folded brains, were more similar than those for the older brain. Younger brains have flatter brains which are probably easier to segment.

Relation to other approaches

Our work is the first to apply a wide range of 3D global folding measures to *in-vivo* clinical data over a critical age range of cortical development (28–37 weeks) not previously studied with curvature. As mentioned in Section 1, during the period of 26–36 weeks gyrification is undergoing many important changes [Raybaud et al., 2003, Encha-Razavi and Sonigo, 2003]. In an earlier study [Batchelor et al., 2002] seven gyrification measures (four based on curvature) were used to assess folding in 10 *ex-vivo* fetal brains; gestational ages were 19–40 weeks, but the majority of cases were less than 23 weeks. More recently, an automated 3D approach [Cachia et al., 2007] based on a measure called Global sulcal index was developed. It is defined as the percentage ratio of the total sulcal area and the outer cortex area; the outer cortex was defined as a smooth envelope of the GM/CSF boundary. The measure is similar to 3D Gyrification Index.

We studied folding on the CSF/GM interface and on the GM/WM interface. An advantage of using the GM/WM in addition to cortical CSF/GM is that some abutting gyral crowns (i.e. touching of adjacent gyri along their borders) may open up when using the GM/WM. [Sisodiya et al., 1996] analyzed folding in GM/WM to study aging in adults and [Pienaar et al., 2006, Dubois et al., 2007] on neonates. [Batchelor et al., 2002, Xu et al., 1999, Tosun et al., 2004] quantified folding on the layer corresponding to the geometric center of the cortex, i.e. the midline between CSF/GM and GM/WM, which approximately corresponds to cortical layer IV. The original motivation for the selection of the midline was the creation of 2D cortical maps [Van Essen and Maunsell, 1980]. The aim was to identify a layer for which a unit surface area anywhere in the map would represent the same amount of cortex (in terms of cortical volume). However, it is not clear whether this concern applies to the current application, where the aim is the extraction of surface shape information. Methods that efficiently identify all problematic instances of infolding remain to be developed [Magnotta et al., 1999].

Our methodology computes curvature directly on the image intensities. Others [Magnotta et al., 1999, Cachia et al., 2003, Toro and Burnod, 2003, Manguin et al., 2004, Batchelor et al., 2002, Luders et al., 2006, Dubois et al., 2007] have computed curvature on 3D triangular meshes, created to approximate the brain surface. Computation of curvature [Gatzke and Grimm, 2006, Rusinkiewicz, 2004] from a triangular mesh can be done with the so called direct methods, which imply direct approximation of a curvature (or of a curvature tensor) within a neighborhood of a point (low computational cost), or by surface fitting, which involves finding an analytic equation that fits the mesh locally (high computational costs). Serious consideration needs to be given to various factors that will influence the quality of the curvature estimation; for example: the number, size, and regularity of the triangles, and surface noise. Different approaches might even be required to compute each type of local curvature [Surazhsky et al., 2003]. Our curvature estimation approach has the advantage that it does not require the polygonalization of the surface or the local fit of a patch. However, the proposed gyrification measures are not dependent on the methodology to compute local curvature, and can be used in a framework based on meshes.

Future work

This work was based on twelve premature infants who exhibited only mild pathology. There is an obvious need to apply the gyrification measures in a larger cohort, to further investigate the sensitivity of the measures and whether the linear model is sustained. Most importantly, we specifically wish to examine whether pathologies such as white matter lesions or ventriculomegaly influence folding measures. A formal verification of the area-independence property is planned, as well as further analysis of current normalization factors.

5 Conclusions

The proposed new and normalized measures provide with a new tool for the in-vivo 3D assessment of global and regional cortical folding, independent of the overall surface area. The measures are applicable to developing a model that tracks development in premature infants. The proposed T-normalized measures are recommended for CSF/GM surfaces; H -normalized measures, GS , AF_H , or 3D GI can be used for GM/WM surfaces.

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Appendix

Appendix: Surface curvature

The most important concept that characterizes curves and surfaces is curvature [Dodson]. In simple terms, (Gaussian) curvature is a scalar measure of the rate of change of direction of a unit normal vector around a surface. A plane has zero curvature because its normal vector is constant.; a sphere has constant curvature everywhere because the unit vector normal changes at a constant rate. Curvature values can be zero, positive or negative. Figure 16 shows an example of the three cases: a hyperboloid with negative curvature, a plane with zero curvature, and a sphere with positive curvature. Given the tangent plane of a surface [Dodson], a point has positive curvature if the surface lies on the same side as the tangent plane. If the tangent plane crosses the surface, curvature is negative.

The intersection of a surface by a plane defines a planar curve. Consider all the planes that are aligned with the surface normal vector at a given point. The intersection of each of those planes defines a curve on the surface, and the curvature of such a curve at that given point is called normal curvature. Normal curvature ranges between a maximum value k_1 and a minimum value k_2 , and are called principal curvatures. The cutting planes related to the curves producing the principal curvatures are orthogonal to each other. Two important shape descriptors are defined based on these principal curvatures: the mean curvature, which corresponds to the average of

the principal curvatures $H = \frac{k_1 + k_2}{2}$, and the Gaussian curvature, which is the product of the principal curvatures $K = k_1 \cdot k_2$. A graphical example of how principal curvatures, mean curvature, and Gaussian curvature change on a surface is shown in Figure 17.

Gaussian curvature is an intrinsic property of the surface and is independent on how it is embedded in space. It gives information of how a surface curves intrinsically, seen as if standing on the surface [Dodson]. On the other hand, mean curvature is a property understood from the surrounding space of the surface, i.e. away from it. There are surfaces, the minimal surfaces, whose characteristic is to have mean curvature zero. This means that at each point the surface should be positively curved in one principal direction and negatively curved in the

perpendicular direction because, by definition, mean curvature is the average of perpendicular curves. A catenoid is an example of a shape with mean curvature zero at each point.

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Fig. 1.
Example of the segmentation of the GM/CSF interface (left) and the GM/WM interface (right).

Fig. 2. Variation of folding and size for the inversely proportional set

Coronal slices from CSF/GM (top) and GM/WM (bottom) iso-surfaces extracted at tissue occupancy (from left to right) of 10%,30%,50%,70%,90%.

Fig. 3.
A depiction of a manual trace of the inner surface (black) and outer surface (gray) of a brain, which resembles the example in [Zilles et al., 1988].

Fig. 4. 3D semi-convex hull (gray) overlaid on the brain volume at 50% tissue occupancy (black) delimited by the CSF/GM interface (top) and GM/WM interface (bottom). From left to right, the 3D semi-convex hull at 10, 40, and 160 iterations.

Fig. 5. Local curvature: proportional set

Maps of local mean curvature (H) for GM/WM at 50% tissue occupancy for three infants ages 28, 32.4, and 36.4 weeks. Positive curvature is displayed as light gray intensities and negative curvature as dark gray intensities (see Footnote 2 on page 15).

Fig. 6. Quantification of folding on 15 whole brains: proportional set
 Plots of twelve folding measures against age for CSF/GM (in gray) and GM/WM (in white).
 Linear fit and 95% confidence intervals are shown.

Fig. 7. Geometrical properties and normalization factors on 15 whole brains: proportional set
Plots for CSF/GM (gray) and GM/WM (white).

Fig. 8. Local curvature: inversely proportional set

Maps of mean curvature for GM/WM at 10%, 50%, 90% tissue occupancy for a 28 week old infant. Positive curvature is displayed as light gray intensities and negative curvature as dark gray intensities (see Footnote 2 on page 15).

Fig. 9. Quantification of folding for whole brains: inversely proportional set
Plots of 12 folding measures against tissue occupancy for CSF/GM (gray) and GM/WM (white).

Fig. 10. Geometric properties and normalization factors: inversely proportional set
Plots for CSF/GM (gray) and GM/WM (white).

Fig. 11. Quantification of folding on left and right hemispheres: proportional set

Plots of folding percentage difference indexes for left (+) and right (o) hemisphere for six folding measures on CSF/GM iso-surfaces at 50% tissue occupancy. Note that the indexes for the old measure *MLN* are distributed around 0.5, while for the new measures are distributed around 0.

Fig. 12. 3D Gyrification Index: proportional set

The first plot shows 3D *GI* for CSF/GM (gray) and GM/WM (white). Linear fit and 95% confidence intervals are shown. The area of the CSF/GM surface and its outer contour (*) at 20 iterations is shown in the center, and those for GM/WM at 40 iterations is shown on the right.

Fig. 13. 3D Gyrification Index: inversely proportional set

The first plot shows the 3D Gyrification Index for CSF/GM (gray) and GM/WM (white). The area of the CSF/GM surface and its outer surface (*) is shown in the center, and those for GM/WM on the right.

Fig. 14. Segmentation assessment: proportional set

Plots of five folding measures against age for GM/WM iso-surfaces at 50% tissue occupancy. The asterisks represent the four repeated segmentations for the two infants aged 29.1 and 32.4 weeks.

Fig. 15. Visual segmentation assessment by overlay: proportional set

Sample slices of three difference volumes created from the overlay of a reference segmentation to three other independent segmentations. The first three columns represent the same sample slice from each of the three difference volumes; the second triplet represents another slice. The first row shows results for the 29.1 week-old infant and the second row for the 32.4 week-old infant. Black dots are the voxels present on one segmentation but not on the other; the gray voxels represent the converse case. The smaller the amount of dots appearing on a brain boundary in this figure, the larger the similarity between two overlapping segmentations.

Fig. 16. Curved surfaces

The hyperboloid (left) is an example of a surface with negative curvature; the plane (center) has zero curvature, and the sphere (right) has positive curvature.

Fig. 17. Maps of k_1k_2K (first row) and H (second row) overlaid on a geometrical shape. Positive curvature is displayed as light gray intensities and negative curvature as dark gray intensities (see Footnote 2 on page 15).

Table 1

Area-dependent 3D measures of surface folding

L^2 norm of curvature	$MLN = \frac{1}{4\pi} \sum_A H^2$	[Batchelor et al., 2002]
	$GLN = \frac{1}{4\pi} \sqrt{A \sum_A K^2}$	
Intrinsic curvature index	$ICI = \frac{1}{4\pi} \sum_A K^+$	[Van Essen and Drury, 1997]
Folding Index	$FI = \frac{1}{4\pi} \sum_A k^{\ddagger}$	[Van Essen and Drury, 1997]
Roundness	$Rn = \frac{A}{\sqrt[3]{36\pi V^2}}$	[Batchelor et al., 2002]
Average curvature	$\overline{H}^{\circ} = \frac{1}{A} \sum_A H^{\circ}$	[Magnotta et al., 1999]
	$\overline{K}^{\circ} = \frac{1}{A} \sum_A K^{\circ}$	

Notation: $k^{\ddagger} = |k_1| (|k_1| - |k_2|)$ and the superscript $^{\circ}$ refers to $^+$ or $^-$.

Table 2
Area-independent 3D measures of surface folding

T-normalized		
L^2 norm of curvature	$ML\ N_T = \frac{T^2}{A} \sum_A H^2$	prv
	$GL\ N_T = T \sqrt[4]{\frac{1}{A} \sum_A K^2}$	prv
Intrinsic curvature index	$ICI_T = T \sqrt{\frac{1}{A} \sum_A K^+}$	prv
Folding Index	$FI_T = T \sqrt[4]{\frac{1}{A} \sum_A k^{\frac{4}{3}}}$	prv
Diff. of ppal. curvatures	$\Delta k_T = \frac{T}{A} k_1 - k_2 $	prv
Average curvature	$\overline{H}_T^o = \frac{T}{A} \sum_A H^o$	prv
	$\overline{K}_T^o = T \sqrt{\frac{1}{A} \sum_A K^o}$	prv
Global curvedness	$GC_T = \frac{T}{A} \sum_A c$	new
Ratio of curvatures	$SH2SH_T = T \sum_A H^2 / \sum_A H$	new
	$SK2SK_T = T \sqrt{\sum_A K^2 / \sum_A K}$	new
H-normalized		
L^2 norm of H	$ML\ N_H = \frac{1}{ H } \sqrt{\sum_A H^2 / A}$	prv
Global curvedness	$GC_H = \frac{1}{A H } \sum_A c$	new
Others		
Global shape index	$GS = \frac{1}{A} \sum_A s$	new
Ratio of areas	$AF_i = A_i / A, i \in \{H^o, K^o\}$	new
Gyrification Index	$GI = \frac{\sum \text{Length inner contour}}{\sum \text{Length outer contour}}$	

Notation: $k^{\frac{4}{3}} = |k_1|(|k_1| - |k_2|)$, c =curvedness, s =shape index. The superscript o refers to $^+$ or $^-$ and AH^o to the area of the surface with H^o curvature (same for K^o). The label 'new' identifies the proposed new measures and 'prv' the normalized versions of previously defined measures.

Table 3
Relationship of folding and age in whole brains: proportional set

		Goodness-of-fit (R^2) of the linear regression	
		GM/CSF	GM/WM
T-normalized measures			
L^2 norm of curvature	MLN_T	0.80	0.07
	GLN_T	0.79	0.21
Intrinsic curvature index	ICI_T	0.83	0.005
Folding Index	FI_T	0.85	0.19
Diff. of ppal. curvatures	Δk_T	0.85	0.001
Average curvature	$\overline{H}_T^+$	0.85	0.10
	$\overline{H}_T^-$	0.72	0.07
	$\overline{K}_T^+$	see ICI_T	see ICI_T
	$\overline{K}_T^-$	0.85	0.27
Global curvedness	GC_T	0.84	0.004
Ratio of squared and average curvature	$SH2SH_T$	0.76	0.25
	$SK2SK_T$	0.69	0.44
H-normalized measures			
L^2 norm of curvature	MLN_H	0.48	0.94
	GLN_H	0.41	0.11
Global curvedness	GC_H	0.54	0.93
Others			
Global shape index	GS	0.61	0.93
Area fraction	AF_{H-}	0.63	0.93
	AF_{K-}	0.44	0.006