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A Cortical Shape-Adaptive Approach to Local Gyrification Index

Ilwoo Lyu^{a,*}, Sun Hyung Kim^b, Jessica B. Girault^b, John H. Gilmore^b, and Martin A. Styner^{a,b}

^aDepartment of Computer Science, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

^bDepartment of Psychiatry, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Abstract

The amount of cortical folding, or gyrification, is typically measured within local cortical regions covered by an equidistant geodesic or nearest neighborhood-ring kernel. However, without careful design, such a kernel can easily cover multiple sulcal and gyral regions that may not be functionally related. Furthermore, this can result in smoothing out details of cortical folding, which consequently blurs local gyrification measurements. In this paper, we propose a novel kernel shape to locally quantify cortical gyrification within sulcal and gyral regions. We adapt wavefront propagation to generate a spatially varying kernel shape that encodes cortical folding patterns: neighboring gyral crowns, sulcal fundi, and sulcal banks. For that purpose, we perform anisotropic wavefront propagation that runs fast along the gyral crowns and sulcal fundi by solving a static Hamilton-Jacobi partial differential equation. The resulting kernel adaptively elongates along gyral crowns and sulcal fundi, while keeping a uniform shape over flat regions like the sulcal banks. We then measure local gyrification within the proposed spatially varying kernel. The experimental results show that the proposed kernel-based gyrification measure achieves a higher reproducibility than the conventional method in a multi-scan dataset. We further apply the proposed kernel to a brain development study in the early postnatal phase from neonate to 2 years of age. In this study we find that our kernel yields both positive and negative associations of gyrification with age, whereas the conventional method only captures positive associations. In general, our method yields sharper and more detailed statistical maps that associate cortical folding with sex and gestational age.

Abstract

*Corresponding author: ilwoolyu@cs.unc.edu (Ilwoo Lyu).

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Keywords

adaptive kernel; early brain development study; local gyrification index; static Hamilton-Jacobi partial differential equation; sulcal and gyral curves; wavefront propagation

1. Introduction

Cortical gyrification is a dynamic process involving cortical expansion, sharpening of gyri and deepening of sulci in early brain development, followed by flattening and opening of sulci and narrowing of gyral crowns with aging (Zilles et al., 1988, 1989; Armstrong et al., 1995). The process of gyrification is often studied from a maturational perspective by tracing global or local developmental trajectories over time. Additionally, it has been shown that local cortical gyrification is related to brain development (Zilles et al., 1988; Armstrong et al., 1995; Luders et al., 2004; Lui et al., 2011; Li et al., 2014b; Kim et al., 2016) and pathological disorders (Schmitt et al., 2002; Harris et al., 2004; Gaser et al., 2006; Schaer et al., 2008; Lebed et al., 2013). A key component that varies across cortical folding studies is the definition of cortical regions over which the gyrification quantified. The main challenge in that regional definition is the cortex shape and its folding, which are highly complex and variable

Initial attempts to quantify cortical gyrification were made by observations of cortical folding changes during mammalian evolution from postmortem data (Jerison, 1961; Elias and Schwartz, 1969). These studies assumed that the cortical surface was deformed from an initial simple zero order surface (outer hull) during evolution. In later work (Zilles et al., 1988; Moorhead et al., 2006), the gyrification index was developed to quantitatively measure the cortical folding by computing a ratio between the pial and outer-hull perimeters on a slice-by-slice basis from structural T_1 -weighted MR images. Although this provides an intuitive interpretation of cortical folding by globally capturing the amount of overall cortical folding, the slice-wise 2D analysis is inherently biased by the cutting plane selection and is expected to underestimate the cortical folding as complex folded sulci are unlikely captured in a single 2D slice. Consequently, approaches have shifted to a 3D surface-based representation (Dale et al., 1999; Van Essen et al., 2001) that provides a better estimation of cortical surface shape. Several investigations have been made based on various geometric representations of cortical folding rather than gyrification index. In Gaser et al. (2006), local mean curvatures computed over the entire cortex were employed as a surrogate local measurements of cortical folding. Batchelor et al. (2002) investigated several different geometric properties as measures of cortical folding. These geometric representations of cortical folding are well defined and readily available. However, they only provide local shape changes within immediate neighborhood of each surface location (commonly within

less than 1 mm range), and thus they do not provide any folding properties on the scale of a single or multiple sulci and gyri.

To improve global or immediate neighborhood folding measures, the concept of a kernel (patch) has been introduced to define a (relatively large) local cortical region over which the cortical folding measure is computed. In this context, a 3D local gyrification index has been proposed as an area ratio between the outer hull and the pial surface (Toro et al., 2008; Schaer et al., 2008; Su et al., 2013; Lebed et al., 2013; Li et al., 2014b). In this approach, regional quantification of cortical folding is obtained by computing the corresponding average within a local region of the cortex being covered by a geodesic kernel. Similarly, Kim et al. (2016) proposed a novel folding measure called surface complexity index that captures the variability of the local cortical shape within a local region. In all these approaches, regional quantification of cortical folding is obtained by computing the corresponding average within a local region as defined by a kernel. The standard way to define such a kernel employs an Euclidean sphere (Toro et al., 2008; Schaer et al., 2008), geodesic distance (Gaser et al., 2006; Kim et al., 2016), nearest neighborhood-ring (Lebed et al., 2013; Li et al., 2014b) or ROIs (Su et al., 2013) (see Fig. 1 for example kernel shapes).

In general, simple local kernel-based approaches tend to describe global cortical folding patterns reasonably well but do not incorporate the fine details of local cortical shape. Such simple kernel-based measures are sensitive to the kernel size and the quality of surface reconstruction (e.g., degree of surface tessellation). For example, an overly large kernel is employed to completely cover deeply buried sulcal fundi such as the Sylvian fissure, which sacrifices sensitivity (Toro et al., 2008; Schaer et al., 2008; Li et al., 2014b). Moreover, as these methods do not take into account any prior knowledge of sulcal or gyral regions, the kernels merge and eventually smooth out cortical folding measures across multiple sulci over the cortex into a single measurement. Such smoothed multi-sulcal and gyral folding measures may result in non-optimal cortical folding analyses, as cortical regions within a single sulcus (gyrus) are more functionally related than those across multiple sulci (gyri) (Power et al., 2011; Wig et al., 2014). Though Lebed et al. (2013) used a small kernel to improve sensitivity, the small kernel cannot sufficiently cover a highly variable sulcus (e.g., sulcal width or depth). Therefore, a main challenge with the conventional approaches is to determine a proper kernel shape and its size to stay in a single sulcus (gyrus) without significant loss of sensitivity. To date, an investigation into optimal kernel size and shape has not been conducted, and none of the conventional methods currently capture folding patterns appropriately across the entire cortical surface.

In this paper, we propose a novel cortical shape-adaptive kernel for cortical folding analyses with the aim of generating more biologically plausible results as shown in Fig. 1c. Inspired by findings of functional homogeneity within sulci or gyri (Power et al., 2011; Wig et al., 2014), we design the proposed kernel to be spatially varying at sulcal fundi (valleys), gyral crowns (ridge-like regions), and sulcal banks (flat regions). The shape of this kernel is locally adapted in the following way:

- At sulcal fundi and gyral crowns: an elongated kernel along the sulcal fundi and gyral crowns

- At sulcal banks: an isotropic kernel that uniformly covers sulcal banks

In this way, the proposed kernel is more likely to stay along a single sulcus (gyrus) than the conventional kernel even with a sufficiently large kernel size as shown in Fig. 1c. To control the kernel shape, we model its behavior as wavefront propagation over the cortical surface, which encodes the cortical folding properties described above. This necessitates the anisotropic wavefront propagation being performed on the cortical surface with fast propagation speed along the gyral crowns and sulcal fundi. We then employ the proposed kernel to compute a local gyrification index though it would also be well suited for other applications that summarize cortical regional measures. This paper extends our previous work (Lyu et al., 2017) in the following ways: 1) we provide a detailed description of the proposed method, 2) methodological evaluation is included, and 3) we report an investigation into associations between morphological brain development and several demographic effects (age, sex, gestational age) during the early postnatal period from shortly after birth through the first 2 years of age. Figure 2 illustrates a schematic overview of the proposed pipeline.

2. Background - Wavefront Propagation

We briefly review concepts of the wavefront propagation that controls the proposed kernel shape. More technical details are discussed in review literatures (Sethian and Vladimirsky, 2003; Jackowski et al., 2005). In our problem setting, we constrain the domain to be a cortical surface (2-manifold) and focus on speed on its tangent space. Given a surface Ω and its boundary $\partial\Omega$, the minimum travel-time from one (or multiple) source $\in \Omega$ to a point $\mathbf{x} \in \Omega$, $u(\mathbf{x})$, follows the propagation equation for $\exists F \in \mathbb{R}^+$:

$$\begin{aligned} \left\| \nabla u(\mathbf{x}) \right\| F\left(\mathbf{x}, \frac{\nabla u(\mathbf{x})}{\left\| \nabla u(\mathbf{x}) \right\|}\right) &= 1, \quad \mathbf{x} \in \Omega \subset \mathbb{R}^2, \\ u(\mathbf{x}) &= 0, \quad \mathbf{x} \in \partial\Omega, \end{aligned} \quad (1)$$

where F is a positive real-valued propagation speed function. Such a formulation of the wavefront propagation is a static Hamilton-Jacobi partial differential equation (H-J PDE). A special case of the H-J PDE is known as the eikonal equation that solves the wavefront propagation with a constant speed function along every direction. Like several applications (curvature-based speed (Osher and Sethian, 1988), diffusion tensor (Jackowski et al., 2005)), we consider a special form of 2×2 tensor matrix $M(\mathbf{x})$ on the tangent plane such that

$$F\left(\mathbf{x}, \frac{\nabla u(\mathbf{x})}{\left\| \nabla u(\mathbf{x}) \right\|}\right) = \frac{\nabla u(\mathbf{x})^T}{\left\| \nabla u(\mathbf{x}) \right\|} M(\mathbf{x}) \frac{\nabla u(\mathbf{x})}{\left\| \nabla u(\mathbf{x}) \right\|}. \quad (2)$$

If M is symmetric and positive, M is of an elliptic form along its eigenvectors. The wavefront propagation behaves according to the design of the tensor matrix M . In this sense, geodesic distances on manifolds can be obtained via wavefront propagation modeled by a static H-J PDE. If the velocity at each vertex has unit speed, the travel-time is essentially equivalent to the geodesic distance; they are interchangeable. Therefore, by setting $F = 1$ (or

$M = I$, the isotropic propagation at unit speed produces a geodesic distance map to all locations of Ω .

Although efficient Dijkstra-like solvers called fast marching (Tsitsiklis, 1995; Sethian, 1996) are well developed for solving the eikonal equation, general H-J PDEs cannot be directly solved using that solver because the characteristics of the PDEs do not coincide with its gradients (Sethian and Vladimirsky, 2003). As pointed out in Jackowski et al. (2005), therefore, PDEs with proper initial boundary conditions are classically solved by decomposing them into an independent system of ordinary differential equations by the method of characteristics (Ockendon, 2003). However, this classic solution may not exist because the PDEs develop a discontinuity without smoothing constraints. Several alternative numerical approaches to a viscosity solution equipped with additional smoothing term are available as well. Single-pass approaches (Sethian and Vladimirsky, 2003) solve H-J PDEs along the characteristic directions, whereas iterative approaches (Kao et al., 2004; Qian et al., 2007) do in a number of pre-defined directions.

In this work, we use the ordered upwind method having $O(\gamma N \log N)$ complexity akin to Dijkstra's shortest path finding, where N is the number of discrete points over Ω with an upper bound of its anisotropy coefficients γ , proposed by Sethian and Vladimirsky (2003). Briefly, at a given point to be updated, the anisotropy coefficient is employed to estimate the possible numerical domain of dependency.

3. A New Measure for Local Cortical Gyrification

Our objective is to design a cortical kernel that adaptively incorporates cortical folding patterns. In order to create the desired kernel, we perform wavefront propagation over the cortical surface. In this context, the desirable kernel is defined as follows:

- At sulcal fundi and gyral crowns: anisotropic speed faster along the ridges and valleys
- At sulcal banks: isotropic speed in every direction

For that purpose, we design a tensor field for the wavefront propagation over the cortical surface in four main steps: 1) sulcal and gyral region segmentation via sulcal and gyral curve extraction (Lyu and Kim, 2015), 2) cortical region segmentation by computing the geodesic distance (= travel-time) between the sulcal and gyral regions, 3) tensor computation from the travel-time map, and 4) shape-adaptive kernel creation by performing the wavefront propagation over the tensor field. In this framework, we solve respective H-J PDEs for the cortical region segmentation and kernel creation. Figure 3 illustrates an overview of the tensor field computation. The proposed local gyrification index is then computed within the proposed kernel as an area ratio of the cortical surface and the outer hull. The next sections focus on the description of the outer hull surface creation and the steps of the kernel creation.

3.1. Outer Hull Creation and Correspondence Establishment

From the pial surface Ω of a subject, we first create the outer hull and establish a surface correspondence between them. As proposed in Kao et al. (2007), an outer hull that tightly envelops the pial surface is generated by applying a morphological closing operation to a binary volume of the pial surface. Here, we follow the same parameter setting of the morphological operation (a sphere of 15 mm diameter) as used in Schaer et al. (2008). Similar to several studies (Jones et al., 2000; Li et al., 2014b), we then apply the Laplace-based surface evolution method (Lee et al., 2016) to trace sub-voxel accuracy trajectories from the pial surface to the outer hull for correspondence establishment. Such a Laplace-based method guarantees a bijective, smooth correspondence and no intersections across trajectories. Starting from the pial surface vertices, we collect the endpoints of these trajectories touching the outer hull volume to obtain the outer hull surface. Let H denote the outer hull surface for the remainder of this paper. In the experiment, we used the same voxel size for the binary surface representation as the input volume. Note that the proposed method does not require a particular surface reconstruction pipeline; any surface reconstruction pipeline can be used to generate cortical surfaces. In this work, we used FreeSurfer (Dale et al., 1999) for the adult population and the infant cortical surface reconstruction pipeline (Li et al., 2014a) for the early postnatal population.

3.2. Sulcal and Gyrus Curve Extraction

We extract sulcal and gyrus curves to segment the cortical surface into sulcal and gyrus regions. To obtain the sulcal and gyrus curves from the cortical surface, we use the automatic sulcal curve extraction method (Lyu and Kim, 2015) that detects concave regions along which sulcal curves are traced. We further extend the idea to gyrus curve extraction by finding convex regions. The method follows two main steps: 1) sulcal and gyrus point selection and 2) curve delineation by tracing the selected sulcal and gyrus points. Sulcal and gyrus points are first determined by employing the line simplification method (Ramer, 1972; Douglas and Peucker, 1973) that prevents the cortical folding patterns from being significantly smoothed out. Sulcal and gyrus curves are then connected as series of neighboring line segments. For the remainder of the paper, ζ denotes a set of the extracted sulcal and gyrus curves. For better sulcal and gyrus curve extraction performance, we use the pial and white matter surfaces, respectively. We then project the gyrus curves onto the pial surface using a surface correspondence between the pial and white matter surfaces. Figure 3a shows an example of the extracted sulcal and gyrus curves on the pial surface.

3.3. Travel-time Map for Local Cortical Region Segmentation

An adaptive kernel can be obtained via wavefront propagation driven over a tensor field of the cortical surface. In order to define a tensor at any location of the cortex, the entire cortical surface segmentation (i.e., gyrus crowns, sulcal fundi, and sulcal banks) is necessary since every cortical region has a different geometry. This can be achieved by computing a geodesic distance map between the extracted sulcal and gyrus curves, which is equivalently modeled as wavefront propagation where the propagation speed is equal to 1 in every direction at $\forall x \in \Omega$, i.e., travel-time between the sulcal and gyrus curves. Note that this is a special case of the eikonal equation where $F = 1$ as discussed in Section 2. To compute a

travel-time map T from ζ to all the locations of Ω , the points $\in \zeta$ are assigned as sources of the wavefront propagation. By letting $M = I$ in (1), with a boundary condition $T(\mathbf{p}) = 0$ for $\forall \mathbf{p} \in \zeta$, the speed function (2) becomes

$$F\left(\mathbf{x}, \frac{\nabla T(\mathbf{x})}{\|\nabla T(\mathbf{x})\|}\right) = 1. \quad (3)$$

For $M = I$, this simplifies the static H-J PDE (1) to

$$\|\nabla T(\mathbf{x})\| = 1. \quad (4)$$

The solution provides a travel-time (geodesic distance) map T for all locations of the surface as illustrated in Fig. 3b.

3.4. Tensor Field

We compute a tensor field over Ω from T to guide the generation of the adaptive kernel. This kernel is designed to become more anisotropic as it reaches sulcal and gyral regions. The tensor field consists of two components: principal propagation directions and associated propagation speeds.

3.4.1. Principal Propagation Direction—In order to compute the tensor field, we need to first determine the two orthogonal directions along which the propagation is performed. The basic idea is to utilize the orthogonal and tangent directions to the sulcal and gyral curves. However, since these curves exist only along sulcal fundi and gyral crowns, we need additionally define these directions in non-curve regions. For this purpose, we use the iso-travel-time contours of T . This modeling issue can thus be addressed by finding shortest trajectories (orthogonal to the contours) of T between sulcal fundi and gyral crowns. As discussed in Sethian and Vladimirsky (2003), the shortest trajectory is computed by tracing characteristic directions rather than gradients for anisotropic equations. For the eikonal equation, however, the directions become coincident. Thus, as T encodes the minimum travel-times from the sources, we can compute the shortest geodesic trajectories along the gradient field ∇T .

For a given point $\mathbf{x} \in \Omega$, its two principal propagation directions $\mathbf{v}_1(\mathbf{x})$, $\mathbf{v}_2(\mathbf{x})$ are defined on the tangent plane by letting

$$\mathbf{v}_1(\mathbf{x}) = \frac{\nabla T(\mathbf{x})}{\|\nabla T(\mathbf{x})\|} \text{ and } \mathbf{v}_2(\mathbf{x}) = \frac{\nabla T^\perp(\mathbf{x})}{\|\nabla T^\perp(\mathbf{x})\|}, \quad (5)$$

such that $\nabla T(\mathbf{x}) \perp \nabla T^\perp(\mathbf{x})$. $\mathbf{v}_1$ encodes the tangent direction to the geodesic trajectory between the corresponding sulcal fundus and gyral crown, and $\mathbf{v}_2$ represents the orthogonal direction to $\mathbf{v}_1$. In a triangulated mesh, we utilize the mean curvature normal approximation by minimizing the Dirichlet energy using Meyer et al. (2003), and a local gradient $\nabla T(\mathbf{x})$ is

then obtained by the weighted mean of the projected first-order directional derivatives (Zaharescu et al., 2009). Figure 3c illustrates an example of ∇T .

3.4.2. Principal Propagation Speed—The second modeling issue is to determine the speed associated with the principal propagation direction at two cortical region types: sulcal fundi/gyral crowns and sulcal banks. For the former type, it is desirable that the speed has minimum and maximum along $\mathbf{v}_1$ and $\mathbf{v}_2$, respectively, which yields an elongated kernel shape as a result. On the other hand, the speed needs to be the same along every direction in the sulcal bank to produce an isotropic kernel shape. For that purpose, a proper normalization of T is needed since locations at the middle of sulcal banks do not possess the same travel-time T ; it varies at the sulcal depth of the corresponding sulcus. We thus normalize T from the sulcal and gyral curves to the middle of sulcal banks. At the end of this, both the normalized travel-time and its reciprocal form are used to define anisotropic speed along the principal propagation directions as well as to control the amount of its anisotropy. Therefore we bound the minimum normalized travel-time by η to control the speed without numerical degenerative conditions ($0 < \eta \leq 1$).

Specifically, we first compute the maximum travel-time among the shortest trajectories passing through a given point and then normalize the travel-time at that point by the local maximum. Specifically, from a given point $\mathbf{x} \in \Omega$, its source $\mathbf{s}_{\mathbf{x}} \in \zeta$ is obtained by tracing gradients over $-\nabla T$ until $T = 0$ while holding $T > 0$ and $T(\mathbf{x}) > T(\mathbf{x} - \nabla T d\mathbf{x})$. This gives a label map of Ω that represents the source of any point $\in \Omega$. Let $D_L(\mathbf{s})$ denote a region of Ω labeled by the same source $\mathbf{s} \in \zeta$, i.e., $D_L(\mathbf{s}) = \{\mathbf{x} \in \Omega | \mathbf{s}_{\mathbf{x}} = \mathbf{s}\}$. Similarly, the maximum travel-time through $\mathbf{x}$ is obtained by tracing over $\nabla T(D_L(\mathbf{s}_{\mathbf{x}}))$ until it touches a boundary of $D_L(\mathbf{s}_{\mathbf{x}})$. The normalized travel-time map S is thus obtained via simple linear interpolation.

$$S(\mathbf{x}) = (1 - \eta) \cdot \frac{T(\mathbf{x})}{T_{\max}(\mathbf{x})} + \eta, \quad (6)$$

where

$$T_{\max}(\mathbf{x}) = \max_{\mathbf{y} \in D_L(\mathbf{s}_{\mathbf{x}})} T(\mathbf{y}). \quad (7)$$

$T_{\max}(\mathbf{x})$ is the maximum travel-time along the shortest trajectory from the source through $\mathbf{x}$ and holds $T(\mathbf{x}) \leq T_{\max}(\mathbf{x})$. Thus, the normalized travel-time map S captures the region types in an easy way; for example, $S(\mathbf{x}) = 1$ if it belongs to the middle of a sulcal bank, as shown in Fig. 3d. We can now consistently assign S and S^{-1} to the speed associated with $\mathbf{v}_1$ and $\mathbf{v}_2$, respectively. They are reciprocal to each other to guarantee the amount of the propagation at any point in Ω is constant, which is equal to 1.

3.4.3. Tensor Matrix—From (5) and (6), the tensor matrix $\tilde{M}(\mathbf{x})$ is defined on the tangent plane as

$$\tilde{M}(\mathbf{x}) = S(\mathbf{x}) \cdot \mathbf{v}_1(\mathbf{x})\mathbf{v}_1(\mathbf{x})^T + S(\mathbf{x})^{-1} \cdot \mathbf{v}_2(\mathbf{x})\mathbf{v}_2(\mathbf{x})^T. \quad (8)$$

The tensor matrix $\tilde{M}(\mathbf{x})$ ultimately guides the spatial-varying wavefront propagation. We recall η is used to prevent M from being degenerative. The minimum bound η is thus employed as a regularization term. Furthermore, the static H-J PDE governed by (8) is convex because it holds the Lipschitz-continuity that bounds the propagation speed F such that $0 < \eta \leq S \leq F \leq S^{-1} < \infty$. As stated in Sethian and Vladimirsky (2003), therefore, the propagation converges to a viscosity solution at the bounded propagation speed F . Note that the speed tensor $\tilde{M}$ becomes isotropic when $\eta = 1.0$. Figure 4 shows behaviors of the proposed kernel varying in η .

3.5. Adaptive Kernel and Local Gyrfication Index

The adaptive kernel at $\mathbf{x} \in \Omega$ is straightforwardly created by solving a static H-J PDE equipped with the proposed tensor matrix $\tilde{M}$ (8). We use the cortical surface Ω to define the kernel specifically suitable to cortical folding while the kernel size is determined on the outer hull H . In this sense, the wavefront propagation is performed over Ω to create a cortical shape-adaptive kernel while the kernel is simultaneously projected by f onto the corresponding locations of H to determine the kernel size (see Fig. 5). Formally, the wavefront propagation guided by $\tilde{M}$ is formulated via a static H-J PDE that satisfies the following equation with a boundary condition $K(\mathbf{x}) = 0$ such that

$$\left\| \nabla K(\mathbf{x}) \right\| \cdot \left(\frac{\nabla K(\mathbf{x})^T}{\left\| \nabla K(\mathbf{x}) \right\|} \tilde{M}(\mathbf{x}) \frac{\nabla K(\mathbf{x})}{\left\| \nabla K(\mathbf{x}) \right\|} \right) = 1. \quad (9)$$

Once travel-time K is computed, we can create a kernel by tracing one of the iso-travel-time contours of K . We denote a bijective function between Ω and H by $f: \mathbb{R}^3 \rightarrow \mathbb{R}^3$. Recall that f is established via a Laplace-based method so it is differentiable. To select a proper iso-travel-time contour at $\mathbf{x}$ for the adaptive kernel creation, we project all the iso-travel-time contours of K onto H via f . Then, we pick a projected iso-travel-time contour such that the area contained by the contour over H is equal to some positive constant (typically, a user-defined parameter). We assume that Ω is well defined with a valid parametrization represented by $\varphi: \mathbb{R}^2 \rightarrow \mathbb{R}^3$ such that $\varphi(u, v) = (x(u, v), y(u, v), z(u, v)) \in \Omega$. Given K and travel-time $\delta \in \mathbb{R}^+$, we formulate the corresponding area of H to the iso-travel-time contour ($T = \delta$) as the following surface integral.

$$A_H(\mathbf{x}; \delta) = \iint_{D_A(\mathbf{x}; \delta)} \left\| \frac{\partial(f \circ \varphi)}{\partial u} \times \frac{\partial(f \circ \varphi)}{\partial v} \right\| du dv, \quad (10)$$

where $D_A(\mathbf{x}; \delta) = \{(u, v) \in \mathbb{R}^2 | K(\varphi(u, v)) = \delta\}$. Our resulting kernel is then determined by fixing the corresponding area of H by finding δ such that $A_H(\mathbf{x}; \delta)$ is equal to some constant

function $\rho(\delta) \in \mathbb{R}^+$. Once δ is obtained by solving (10), we can compute the surface area of Ω governed by δ as follows.

$$A_{\Omega}(\mathbf{x}; \delta) = \iint_{D_A(\mathbf{x}; \delta)} \left\| \frac{\partial \varphi}{\partial u} \times \frac{\partial \varphi}{\partial v} \right\| du dv. \quad (11)$$

From (10) and (11), the proposed local shape-adaptive gyrification index is then given by the area ratio

$$lGI(\mathbf{x}; \rho(\delta)) = \frac{A_{\Omega}(\mathbf{x}; \delta)}{A_H(\mathbf{x}; \delta)} = \frac{1}{\rho(\delta)} A_{\Omega}(\mathbf{x}; \delta). \quad (12)$$

The local surface area for each vertex is approximated by using barycentric cells in a triangulated mesh. Figure 5 shows the different kernels applied to the adult human cortex at $\rho = 316 \text{ mm}^2$.

4. Validation

The proposed local gyrification index is determined by two parameters η and ρ . We performed experiments on healthy control datasets and characterized the behaviors of the proposed kernel by varying η and ρ . In the experiment, we created pial cortical surfaces using the standard Freesurfer pipeline (Dale et al., 1999). We evaluated the proposed method on the left hemispheres at a fine sampling of 163,842 points (uniform sampling in spherical parametrization via icosahedron subdivision) to evaluate performance of the local gyrification index in terms of reproducibility and sensitivity.

4.1. A Choice of Kernel Size

It is important to cover sulcal and gyral regions completely to capture sulcal folding appropriately. We computed the minimal kernel size from a given subject population. It is noteworthy that the outer hull squeezes the sulcal regions while leaving the gyral crown with subtle distortion because the correspondence to the outer hull is obtained by the Laplace-based evolution. We thus focused on the outer hull area A_H that corresponds to the sulcal fundi. To determine the minimal kernel size that fully spans a sulcal region (i.e., at least two gyral crowns), we compute A_H for $\forall \mathbf{x} \in \Omega$ belonging to the sulcal curves. Since cortical area varies across subjects, we normalized the kernel size with the average total cortical surface area over the population to remove the impact of overall cortical size.

We used the Kirby dataset on 21 healthy volunteers as described in Landman et al. (2011), available on NITRC. Scan-rescan imaging sessions with T_1 -weighted scans were acquired using an MP-RAGE sequence on the 21 subjects. To improve measurement accuracy, we used the average local gyrification index for each subject between the scan and rescan sessions. We chose $\rho = 316.66 \text{ mm}^2$ over the population to guarantee that the kernel size completely covers any sulcus in this subject population. Figure 6 and Figure 7 shows local gyrification indices using different kernel sizes. The proposed kernel captures the cortical

folding more adaptively especially using a small kernel size. Despite a high blurring effect with a large kernel, the proposed adaptive kernel provided comparable local gyrification indices over the entire cortex especially at the central or cingulate sulcus, for example.

4.2. Reproducibility

We evaluated the reproducibility of the proposed local gyrification index using a large set of scan-rescan data. A human phantom (male, age 26 at the start of this study) was scanned at the four different imaging sites, equipped with a Siemens 3T Tim Trio scanner (Siemens, Erlangen, Germany) for evaluation, at irregular intervals over the period of 2.5 years. The same scanning sequences were employed for all the MRI scans and 36 scans were acquired in total. We quantitatively evaluated the proposed method without and with the outer hull correspondence.

4.2.1. Local Kernel Shape—We first evaluated the kernel reproducibility itself without including the outer hull correspondence. For this purpose, we aligned all the cortical surfaces via a rigid alignment (Besl et al., 1992). We then computed a kernel with a fixed size on the pial surface and measured the average closest distance for every possible pair (36×35 combinations in total) of the acquired kernel boundaries at the corresponding locations from different scans. Such extensive comparisons were made because no ground truth of boundary correspondence is available and the metrics are asymmetric (one-sided) in general. For each kernel size from 316 to 1,264 mm^2 with an interval of 316 mm^2 , we varied $\eta = 1.0, 0.5, 0.2$, and 0.1. The average closest distance over the entire cortex are summarized in Table 1. The result revealed that the boundaries of the corresponding kernels were almost completely overlapping as measured by the average closest distance that differs less than a single triangle edge. This is due to the utilization of the discrete wavefront propagation whose boundary stops at a discrete vertex on the triangulated surface. In terms of the triangulated size of the pial surface (average edge length: $1.16 \pm 0.46 \text{ mm}$), however, this implies that our approach was able to achieve an excellent reproducibility in computing the proposed kernel even at a high anisotropic speed $\eta = 0.1$. We note that the adaptive kernel is becoming more sensitive to the sulcal and gyral curve extraction method as η decreases and thus the average closest distance increases while the resulting reproducibility decreases.

4.2.2. Local Gyrification Index—We computed local gyrification indices using the conventional method (Schaer et al., 2008) and the proposed kernel. We varied the kernel area ρ on the outer hull from 316 to 1,264 mm^2 with an interval of 316 mm^2 for $\eta = 1.0, 0.5, 0.2$, and 0.1. Since the local gyrification index is unitless, we used a coefficient of variation (CoV) to measure the percentage of its measurement error that quantifies how local gyrification indices vary across multiple scans. Figure 8 illustrates the reproducibility over the entire surface for the conventional and proposed methods. Although the reproducibility may be influenced by the surface correspondence f , the proposed local gyrification index achieved a comparable reproducibility to the conventional method for both the isotropic and anisotropic propagation. For the small kernel size (316 mm^2), the conventional method was unstable, as expected, around the Sylvian fissure likely due to its deeply buried sheet whereas the proposed kernel provided a consistently high reproducibility even in this difficult-to-measure cortical area. We note that the isotropic propagation should be

considered as a lower bound of the proposed method as it does not take into account the sulcal and gyral curves for the local gyrification index computation. Table 2 summarizes the average coefficient of variation of the local gyrification index over the entire cortex at different anisotropic speed η . As expected, the local gyrification index has a slightly lower, but still better, reproducibility when using anisotropic propagation due to its increased sensitivity to the variability in the sulcal and gyral curve extraction. Since there is a trade-off between reproducibility and measurement accuracy, we empirically set $\eta = 0.2$ to more adaptively capture cortical folding, while keeping a comparable reproducibility to the conventional method.

5. Application to Brain Development in Early Postnatal Phase

In recent years an increasing number of studies have focused on cortical gyrification in the early postnatal period starting shortly after birth (the neonatal period) through 2 years of age. We focused on employing the proposed local gyrification index to study its relationship with several demographic effects. We investigated the following hypotheses:

1. Cortical gyrification dramatically changes in the first two years of life and exhibits spatially distinct patterns of development.
2. The proposed method reveals novel patterns of associations between local gyrification measures and variables of interest (gestational age, age at scan, sex), especially in sulcal regions, than existing methods.

5.1. The UNC Early Brain Development Studies (EBDS)

This section briefly describes the EBDS dataset¹ collected at the University of North Carolina at Chapel Hill.

5.1.1. MR Image Acquisition—Subjects were part of a large prospective study of early brain development in healthy singletons and twins (Gilmore et al., 2007; Knickmeyer et al., 2008; Gilmore et al., 2010, 2012). Subjects were recruited prenatally and scanned shortly after birth, at age 1, and 2 years. MR Images were acquired on both a Siemens Allegra and a Siemens Timm Trio head-only 3T scanner (Siemens Medical Systems, Erlangen, Germany). Children were scanned during natural, unsedated sleep, fitted with ear protection and swaddled using a vacuum-fixation device to reduce head motion. T_1 -weighted structural pulse sequences were a 3D MP-RAGE (TR = 1,820 ms, inversion time = 1,100 ms, TE = 4.38 ms, flip angle = 7°, resolution = 1 mm × 1 mm × 1 mm). Proton density and T_2 -weighted images were obtained with a TSE sequence (TR = 6,200 ms, TE1 = 20 ms, TE2 = 119 ms, flip angle = 150°, resolution = 1.25 mm × 1.25 mm × 1.95 mm). For neonates who were deemed likely to fail due to difficulty sleeping, a fast T_2 sequence was done with a 15% decreased TR, smaller image matrix and fewer slices (5,270 ms, 104 mm × 256 mm, 50 slices).

¹The Institutional Review Board of the University of North Carolina at Chapel Hill approved this study.

5.1.2. Data Exclusion Criteria—Subjects were excluded if they met at least one of the following conditions: 1) gestational age at birth less than 32 weeks, 2) the length of stay in the neonatal intensive care unit greater than 1 day, 3) abnormality on MRI other than a minor intracranial hemorrhage, common in the neonatal period (Looney et al., 2007), 4) major medical or neurologic illness after birth, 5) high familial risk for schizophrenia and bipolar disorder. In the EBDS dataset about 30% of the entire population is at familial risk for psychiatric illness, as these subjects were specifically recruited as part of another line of research in the EBDS. In this study we only considered singleton subjects. Table 3 summarizes the final dataset of subjects meeting the above criteria that were included in this study.

5.1.3. Surface Model Reconstruction and Local Gyrification Index—The surface models were reconstructed via the infant cortical surface reconstruction pipeline (Li et al., 2014a) and were resampled at 163,842 vertices via a standard icosahedron subdivision. The surface correspondence was established using the group-wise surface correspondence method (Lyu et al., 2013, 2015). In the morphological operation for the outer hull creation, we scaled the image size to the average adult human brain, resampled to a prior volume resolution ($256\text{ mm} \times 256\text{ mm} \times 256\text{ mm}$), performed the morphological operation in this adult normalized space, and then rescaled the resulting hull back to the original brain size. This approach ensures that the size of the morphological operator to close all major sulci can be kept consistent across all subjects (a sphere of 15 mm diameter used in this paper). Previous studies have further found that the operator size yields a negligible difference in hull definition when it is increased or decreased in size by as much as 50% (Kao et al., 2007; Schaer et al., 2008). Our method can thus be expected to be reasonably stable to variations in brain size and shape. Since the cortical surface area dramatically changes with age, we further regularized the kernel size based on two observations. First, the experimental results already revealed that the minimal kernel size fully spanning all the sulcal regions on the adult outer surface was roughly 316 mm^2 . Second, in order to take into account the inter-subject variability in cortical surface area, we adaptively rescaled the kernel size for each subject according to its corresponding age group. In the EBDS dataset the average cortical surface areas for neonates, 1-year-olds, and 2-year-olds have scaling factors of 0.36, 0.6, 0.66 compared to an average adult cortical surface area, respectively. Specifically, for both left and right hemispheres, the average kernel size was 108 mm^2 ($r \approx 5.9\text{ mm}$), 180 mm^2 ($r \approx 7.6\text{ mm}$), 200 mm^2 ($r \approx 8.0\text{ mm}$) for neonates, 1-year-olds and 2-year-olds, respectively.

5.2. Linear Mixed-Effects Model for the Longitudinal Study

We designed longitudinal linear mixed-effects models to investigate the association between cortical morphological change (local gyrification change) and several fixed effects in early childhood. The local gyrification index was used as a dependent variable Y , and the fixed effects were composed of 3 covariates: postnatal age at scan, sex, and gestational age at birth. The effects were tested via a longitudinal linear mixed-effects model computed in SurfStat². For each subject i , the following linear mixed-effects models were fitted to our data, with U_i capturing estimates for the subject-specific random effects.

$$Y_i = \beta_0 + \beta_{\text{Age}} \text{Age}_i + \beta_{\text{Sex}} \text{Sex}_i + \beta_{\text{Gest}} \text{Gest}_i + U_i + \varepsilon_i, \quad (13)$$

where ε_i is an error term. In the experiment, a standard false discovery rate (FDR) correction (Benjamini and Hochberg, 1995) was applied to correct for multiple comparisons for models in (13).

5.3. Findings of Early Morphometry

5.3.1. Cortical Gyrification in the Early Postnatal Phase—The statistical analysis revealed that local gyrification was highly associated with age as visualized in Fig. 9. Most cortical regions had a positive rate of change of cortical folding, whereas the deep sulcal regions such as central and cingulate sulci had almost zero (and even negative) rate of change. For the sex effect, male subjects showed persistently higher local gyrification in the visual cortex and right precentral sulcal region, whereas female subjects showed higher gyrification in superior temporal, right inferior frontal lobe, and parieto-occipital sulcal regions, as shown in Fig. 10. For the gestational age effect at birth, the cortical gyrification changed asymmetrically in the left and right hemispheres as illustrated in Fig. 11. Overall, positive associations with the gestational age were revealed over most cortical regions while negative associations were found in the primary motor cortex and collateral fissure.

5.3.2. Comparison with FreeSurfer—The ability of the local gyrification index to reveal statically significant regions is a key feature in the population analysis. In this section, we computed three different local gyrification index measures using the proposed method with the isotropic and anisotropic propagation and FreeSurfer (Schaer et al., 2008). Fig. 12 illustrates the average local gyrification index computed for different age groups. The same kernel size of 800 mm^2 ($r \approx 16 \text{ mm}$) was employed for fair comparisons of age effects (see Fig. 13). Note that 800 mm^2 at age 2 years is a regularized kernel size corresponding to that of the adult human brain as suggested by Schaer et al. (2008). Since the small kernel size of 200 mm^2 worked poorly under the FreeSurfer method (see Fig. 12), i.e., unstable statistics were revealed particularly around deep sulci as shown in Lyu et al. (2017) (see also Fig. 8 for low reliability even on the adult brain), we only used the size of 800 mm^2 for comparisons. The experiment revealed not only that the overall statistical significance over the cortical surface was comparable with FreeSurfer and isotropic propagation but also that the proposed local gyrification index achieved more refined results than FreeSurfer as the proposed index more adaptively captured local gyrification along cortical folds as shown in Fig. 13. Specifically, for the age effect, most sulcal regions showed positive associations with age in FreeSurfer, whereas negative associations were revealed in those sulcal regions by our method. For the sex and gestational age effects, although both methods had largely similar patterns of the statistically significant regions, the proposed method provided finer t -value maps along cortical folds such as the central sulcus.

²SurfStat is a MATLAB toolbox for statistical analysis of cortical surface data employing random field theory for statistical inference (Worsley et al., 2009), publicly available at <http://www.stat.uchicago.edu/faculty/InMemoriam/worsley/research/surfstat/index.htm>

6. Discussion

6.1. Local Gyrification Index

Several metrics have been proposed to measure local cortical gyrification. The most common methods are based on an area ratio of the pial surface over the reference model (e.g., outer hull). Depending on the metric definition, the denominator could be either the reference model or the pial surface. Lebed et al. (2013) used an area ratio reciprocal to the one used in Schaer et al. (2008), for instance, so that a constant kernel over the pial surface captures cortical folding more uniformly. When considering cortical folding evolution from a zero order shape (Jerison, 1961; Elias and Schwartz, 1969), it is more plausible that the amount of cortical folding is measured from the outer hull. A main challenge with these conventional approaches was to find a proper kernel size to cover at least a single sulcus. Either a large kernel was used to guarantee complete coverage of deeply buried sulcal fundi such as the Sylvian fissure (Schaer et al., 2008) sacrificing sensitivity or a small kernel was used (Lebed et al., 2013) that cannot sufficiently cover a highly variable sulcus. Neither method appropriately captures the folding patterns across the entire cortical surface.

The proposed adaptive kernel improves sensitivity while appropriately capturing differently sized cortical folding regions. In contrast to the conventional approaches, the main idea of the proposed framework comes from the wavefront propagation over the pial surface and the Laplace-based correspondence between the pial surface and outer hull. In the conventional method (Schaer et al., 2008), the kernel was determined only on the outer hull, where local cortical folding is difficult to capture. Even with a kernel defined on the pial surface as in Lebed et al. (2013), a large kernel may be needed to span a deeply buried sulcus. To address issues related to kernel creation, the proposed kernel is determined by fixing the corresponding area to the outer hull, while the wavefront propagation is performed over the pial surface to create a cortical shape-adaptive kernel that captures the local cortical shape. Thanks to the Laplace-based correspondence between the pial surface and the outer hull, cortical folding is represented consistently on the outer hull. This renders our method less sensitive to sulcal depth and width as the area of the sulcal fundus is quite small relative to its neighboring gyral regions during the computation of the corresponding outer hull area. This consequently enables the computation of a local gyrification index along sulcal fundi with the anisotropic kernel, providing a more localized measurement as shown in Fig. 6. Furthermore, compared to the isotropic propagation, the local gyrification index can be refined along sulcal fundi and gyral crowns via the proposed anisotropic propagation. For instance, Figure 6 shows that the isotropic propagation produces overly smoothed local gyrification indices at the gyral junction between the central and middle frontal gyrus, which can be improved via the anisotropic propagation. Also, the anisotropic propagation better quantifies the average gyrification indices along the cingulate sulcus even with the large kernel size.

6.2. Cortical Shape-Adaptive Kernel

The proposed shape-adaptive kernel can be defined anywhere on the cortex, so it does not require any particular interpolation scheme to assign a local gyrification index for a given location in contrast to Schaer et al. (2008); Lyu et al. (2016). However, there are two major

issues in the proposed kernel computation related to parameter choice: the amount of anisotropy and the kernel size. As shown in our experiments, there is a trade-off between sensitivity and reproducibility with respect to anisotropy. In terms of sensitivity, cortical folding is better quantified with a higher anisotropic speed, which adaptively captures cortical folding along sulcal fundi and gyral crowns. On the other hand, using a kernel with higher anisotropy is more sensitive to the quality of the sulcal and gyral curve extraction as these curves are the source of the wavefront propagation though it maintains a reproducibility level comparable to that of the conventional method. We note that the conventional method evaluates its local gyrification index within a spherical region that is not of exactly the same disc region at the corresponding location as the intersecting region of the outer hull is usually larger than the corresponding disc region, which leads to a higher blurring effect on the measurements with loss of sensitivity, as pointed out in Schaer et al. (2008). We suggested an anisotropic speed based on the experiment, yet depending on the application, the user can choose alternative parameters to leverage sensitivity and reproducibility.

Another issue is to find the proper kernel size. A large kernel tends to smooth out cortical folding patterns as already demonstrated in several studies. In this work, we used the minimal kernel size that completely covers any of the sulcal fundi. In the experiments on the Kirby dataset, there is a visible blurring effect of cortical folding measures in several sulcal regions, and such a blurring effect is emphasized as the anisotropic speed becomes isotropic. In the present study, that effect is rarely avoidable when using a fixed kernel size across the entire surface due to the variable nature of cortical folding. Though, with the incorporation of the anisotropic wavefront propagation, the blurring effect can be reduced by minimizing the influences of the neighboring sulci. It would be interesting to study if an optimal size could be adaptively determined based on its neighborhood. One way to do so would be to use the spatial information of sulci and gyri where the adaptive kernel size can be computed based on the neighboring gyral and sulcal curves, similar to Lyu et al. (2016). This approach looks promising, but the adaptive kernel size may need to be justified at any point rather than just at sulcal and gyral locations.

There is a single parameter for the sulcal and gyral curve extraction: the tolerance for candidate point filtering in the line simplification. This quantity controls the representation level of the sliced contour at each candidate point, i.e., the deviation between the simplified and original contours. This tolerance value typically shows a similar behavior compared to the choice of sulcal depth thresholding. Depending on a tolerance quantity, the number of the selected sulcal and gyral points varies; the smaller tolerance, the more sulcal and gyral curves are computed. A small tolerance could yield an overestimated travel-time map since additional, shallow sulcal and gyral regions are considered. Although this could result in a different gyrification index map particularly on minor sulcal and gyral branches, the overall local gyrification index map can be consistently represented in the primary cortical folding regions even with a large tolerance value. From a morphological perspective, shallow regions have gyrification index measurements nearly equal to 1, which implies that the propagation type may not considerably affect the resulting gyrification index.

In addition to these parameter choices, a tensor singularity can happen at a single point in the junction region where multi-curves cross each other. However, in the experiments, we observed that the number of such points was small enough on the appropriately tessellated surface (typically, less than 0.5% out of 160k vertices). Most importantly, these locations have a negligible influence on the resulting kernel shape as their associated tensors yield infinitesimal displacements at the locations during the wavefront propagation.

6.3. Computational Issues

There are several computation issues with the proposed kernel creation. First, it is generally time-consuming to compute a local gyrification index for each vertex on the pial surface; for each hemisphere with 160k vertices, it takes about 6 hours and 17 hours on a single thread (Intel Xeon E5-2630 2.20GHz) at $\rho = 316 \text{ mm}^2$ and $1,264 \text{ mm}^2$, respectively. However, such an issue can be handled by a uniform (or shape-adaptive) sampling over the cortical surface to reduce redundancy in overlapping regions that produce almost the same index as their neighboring vertices. The proposed method is of a high scalability including curve extraction, so this can be alternately addressed by parallelizing the entire processing to simultaneously (independently) handle each vertex.

Second, although sulcal and gyral curves in this work were employed as the source of the anisotropic propagation, other information could be used for the travel-time computation. The proposed approach is versatile; one can also incorporate sulcal depth or local curvature as potential candidate sources for the travel-time map computation for example.

Finally, the proposed processing was performed over the discretized surface model from which numerical errors arise. For the surface models we used in the experiment, the average errors in the reproducibility were less than the average edge length ($1.16 \pm 0.46 \text{ mm}$), which was acceptable relative to the original MR image resolution ($1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$). However, this error could be reduced by further approximation of the wavefront propagation at each triangle using a barycentric (or any valid interpolation) technique, which could result in more stable and reliable measurements.

6.4. Cortical Development in the Early Postnatal Phase

Overall, the statistically significant regions revealed by the proposed local gyrification index were roughly in agreement with those of existing methods, while the regions themselves were more refined along local cortical folding, displaying far more detail than existing methods. Additionally, the experimental results from analyses investigating the associations with postnatal age at scan, sex, and gestational age using the proposed method revealed several interesting findings.

First, most cortical regions have both positive and negative associations with age. This observation differs from both Li et al. (2014b) and FreeSurfer that the local gyrification index increases across the entire cortex with age (showing only positive associations with age), whereas our refined analysis revealed that several regions, such as the central motor and cingulate sulci, show negative associations with age during the first two years of life. From a biological perspective, negative associations between postnatal age and local gyrification index may be related to differential growth rates across the cortex in which deep

cortical folding in some regions is already apparent at an early age, while the width between gyral crowns increases over time, yielding a reduction in the gyrification index in those regions. From a methodological perspective, the main reason for the difference between our study and Li et al. (2014b) is due to the sulcal folding-adaptive quantification for the localized analysis where a smaller kernel size is used in the proposed method.

Second, we found that several cortical regions exhibited statistically significant sex and gestational age effects during early brain development. Few studies have focused on the effects of sex and gestational age on cortical gyrification, and to our knowledge, their impact on cortical developmental trajectories still remain unclear in the early postnatal phase. Despite the gap in the literature, associations between sex and gyrification may be reflective of sexually dimorphic brain volume changes during the early postnatal period (Gilmore et al., 2007). It has also been shown that gestational age is a predictor of brain volumes in this age range (Knickmeyer et al., 2016), and thus the relationship between local gyrification and gestational age is likely mediated by brain size. Our proposed method offers the opportunity to probe such associations further, by providing the ability to study how gyrification measures develop across the cortex in a fine-tuned manner that has not been afforded by standard methods for computing measures of cortical gyrification to date.

7. Conclusion

In this paper, we proposed a local gyrification index using a novel cortical shape-adaptive kernel computed via wavefront propagation over the cortical surface. In contrast to a simple geodesic or nearest neighborhood ring-based kernel, the proposed kernel is adaptively elongated along the cortical geometry. The proposed kernel is well formulated by a static H-J PDE with a sufficient condition that guarantees a unique viscosity solution to our specific problem. Sulcal and gyral curves serve as the source of the wavefront propagation to create a travel-time map. The proposed kernel is then guided over the gradient field computed by the travel-time map.

In our experiments, we show that the proposed computation achieves highly reproducible kernels even for in case of highly anisotropic kernels, as well as a reproducibility of the local gyrification index comparable to the conventional method. Finally we show that the resulting local gyrification index measures are close to the ground truth in both shallow and deep sulci using simulation data. For an appropriate shape-sensitivity and reproducibility, we also propose a proper kernel size and anisotropy. The results showed that the proposed kernel adaptively captures local folding patterns in a scan-rescan human dataset for both small and large kernel sizes. Moreover, we presented an application to quantify cortical morphological development in the early postnatal phase, in which a linear mixed-effects model revealed age, sex and gestational age at birth associations with cortical gyrification indices.

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Appendix A.: Evaluation of Simulated Cortical Folding

Due to the high variability in cortical folding, it would be computationally expensive and difficult to model every possible sulcal folding pattern and determine the kernel size that fully contains a single sulcal fundus and gyral crown. For simplicity, we simulated such an ideal scenario for numerical validation, in which the gyral crowns are parallel to the sulcal fundi and symmetric at the sulcal fundus. To create a simple cortical folding model, we started with an implicit plane in the x - and y -parametric space in $\mathbb{R}^2$ given by $(x, y) \in [-\infty, \infty] \times [-0.75, 0.75]$. We then applied a sine wave (amplitude = $a/2$ and wavelength = $1/2$) over such a domain to obtain a sine-waved plane F :

$$F(x, y) = \frac{a}{2} [-\cos(2\pi(2y + 1)) - 1]. \quad (\text{A.1})$$

This gives three identical sulci having the same depth a (see Fig. A.14a). We then modified the magnitude of the middle sulcus $y \in [-0.25, 0.25]$, while fixing $a = 1$ for the others to simulate two different scenarios: shallow ($a = 0.5$) and deep ($a = 2.0$) sulci. A line integral was performed along the sine wave to compute the ground-truth local gyrification indices of shallow, deep, and neighboring sulci, respectively: 2.30, 8.11, and 4.19. To evaluate the proposed kernel independent of a surface correspondence method, we used $(x, y, F(x, y))$ as a corresponding point to $(x, y, 0)$ on the parametric space. We selected the gyral and sulcal points as the sources of the propagation by finding the extreme points of F . The propagation was then performed at the origin of the plane $(0, 0, F(0, 0))$. As η decreases, it took longer propagation time to reach two neighboring gyral crowns, $(0, 0.25, 0)$ and $(0, -0.25, 0)$, proportional to $-\log \eta(1 - \eta)$, whose resulting kernel thus spans more surface area (see Appendix B for details). Figure A.14 shows the two shallow and deep sulci generated by (A.1).

To examine local gyrification index change over η , we measured it on the simulated cortical folding shape for every areal interval proportional to the standardized propagation area, in which the kernel touches the two neighboring gyral crowns. In Fig. A.15, the local gyrification index becomes closer to the ground truth as η decreases due to its increasing anisotropic speed along the sulcal fundus. We further increased the kernel size to almost fully cover the two neighboring sulcal fundi. The local gyrification index became decreasing as the neighboring sulcal fundi increasingly influenced the local gyrification index. For both shallow and deep sulci, the local gyrification index changes slowly as η decreases. This implies that the anisotropic propagation computed the local gyrification index in a more cortical shape-adaptive way than the isotropic propagation.

Figure A.14:

Simulated equally-spaced (a) identical, (b) shallow, and (c) deep sulci with their normalized travel-time maps: sulcal fundus and gyral crown (*blue*) or sulcal bank (*red*). The neighboring sulci are identical with the same depth ($a = 1.0$). The sulcal and gyral regions are selected by finding extreme points as sources of the wavefront propagation. The travel-time map is normalized with respect to the spatial information over the cortical surface.

Figure A.15:

Local gyrification index of the sine-waved plane in two different simulated scenarios: (a) shallower and (b) deeper sulci than the neighboring ones (see Fig. A.14). The ground truth values for both scenarios are shown by dashed line. The local gyrification indices are assessed on the two simulated sulcal depths. When the proposed kernel touches two gyral crowns (standardized area = 1), it gets closer to the ground truth as η decreases (higher anisotropic speed). Since the two neighboring sulcal fundi are deeper than the sulcus being evaluated, the gyrification index increases as the propagation covers more area of the neighboring fundi (*left*), whereas the gyrification index constantly decreases since the neighboring sulcal fundi are shallower than the sulcus being evaluated (*right*).

Appendix B.: Travel-time of Simulated Symmetric Cortical Folding

Consider total travel-time from a sulcal fundus to its neighboring gyral crowns (see Fig. A.14a). The wavefront propagation thus begins at the sulcal fundus of $\mathbf{x}$ such that $T(\mathbf{x}) = 0$. We denote the length of its trajectory to the gyral crown by l with a linear parametrization of $t \in [0, l]$. This encodes that, for example, $t = 0$ corresponds to the sulcal fundus and $t = l$ to the gyral crown. From (6), the travel-time along the gradient directions $\mathbf{v}_1$ is obtained by the inverse of its speed:

$$\int_0^l \frac{1}{(1-\eta)^{\frac{(l/2 - |t - l/2|)}{l/2}} + \eta} dt. \quad (\text{B.1})$$

This is symmetric at $t = l/2$, which yields a closed form by simplifying the original formula (B.1).

$$\begin{aligned} & \int_0^{l/2} \frac{1}{(1-\eta)^{\frac{t}{l/2}} + \eta} dt + \int_{l/2}^l \frac{1}{(1-\eta)^{\frac{(l-t)}{l/2}} + \eta} dt = 2 \int_0^{l/2} \frac{1}{(1-\eta)^{\frac{t}{l/2}} + \eta} dt \quad (\text{B.2}) \\ & = \int_0^1 \frac{1}{(1-\eta)^t + \eta} dt = -l \frac{\log \eta}{1-\eta}. \end{aligned}$$

This implies the minimum travel-time to reach the neighboring gyral crowns from the sulcal fundus given a length of the trajectory between them.

References

- Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K, 1995 The ontogeny of human gyrification. *Cerebral Cortex* 5 (1), 56–63. [PubMed: 7719130]
- Batchelor PG, Smith AC, Hill DLG, Hawkes DJ, Cox TCS, Dean A, 2002 Measures of folding applied to the development of the human fetal brain. *IEEE transactions on medical imaging* 21 (8), 953–965. [PubMed: 12472268]
- Benjamini Y, Hochberg Y, 1995 Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the royal statistical society. Series B (Methodological)*, 289–300.
- Besl PJ, McKay ND, et al., 1992 A method for registration of 3-d shapes. *IEEE Transactions on pattern analysis and machine intelligence* 14 (2), 239–256.
- Dale AM, Fischl B, Sereno MI, 1999 Cortical surface-based analysis: I. segmentation and surface reconstruction. *Neuroimage* 9 (2), 179–194. [PubMed: 9931268]
- Douglas D, Peucker T, 1973 Algorithms for the reduction of the number of points required to represent a digitized line or its caricature. *Cartographica: The International Journal for Geographic Information and Geovisualization* 10 (2), 112–122.
- Elias H, Schwartz D, 1969 Surface areas of the cerebral cortex of mammals determined by stereological methods. *Science* 166 (3901), 111–113. [PubMed: 4897390]
- Gaser C, Luders E, Thompson PM, Lee AD, Dutton RA, Geaga JA, Hayashi KM, Bellugi U, Galaburda AM, Korenberg JR, et al., 2006 Increased local gyrification mapped in williams syndrome. *Neuroimage* 33 (1), 46–54. [PubMed: 16901723]
- Gilmore JH, Lin W, Prastawa MW, Looney CB, Vetsa YSK, Knickmeyer RC, Evans DD, Smith JK, Hamer RM, Lieberman JA, et al., 2007 Regional gray matter growth, sexual dimorphism, and cerebral asymmetry in the neonatal brain. *The Journal of neuroscience* 27 (6), 1255–1260. [PubMed: 17287499]
- Gilmore JH, Schmitt JE, Knickmeyer RC, Smith JK, Lin W, Styner M, Gerig G, Neale MC, 2010 Genetic and environmental contributions to neonatal brain structure: a twin study. *Human brain mapping* 31 (8), 1174–1182. [PubMed: 20063301]
- Gilmore JH, Shi F, Woolson SL, Knickmeyer RC, Short SJ, Lin W, Zhu H, Hamer RM, Styner M, Shen D, 2012 Longitudinal development of cortical and subcortical gray matter from birth to 2 years. *Cerebral Cortex* 22 (11), 2478–2485. [PubMed: 22109543]
- Harris JM, Yates S, Miller P, Best JJ, Johnstone EC, Lawrie SM, 2004 Gyrification in first-episode schizophrenia: a morphometric study. *Biological psychiatry* 55 (2), 141–147. [PubMed: 14732593]
- Jackowski M, Kao CY, Qiu M, Constable RT, Staib LH, 2005 White matter tractography by anisotropic wavefront evolution and diffusion tensor imaging. *Medical image analysis* 9 (5), 427–440. [PubMed: 16040268]
- Jerison HJ, 1961 Quantitative analysis of evolution of the brain in mammals. *Science* 133 (3457), 1012–1014. [PubMed: 13789972]
- Jones SE, Buchbinder BR, Aharon I, 2000 Three-dimensional mapping of cortical thickness using laplace's equation. *Human brain mapping* 11 (1), 12–32. [PubMed: 10997850]
- Kao C-Y, Hofer M, Sapiro G, Stern J, Rehm K, Rottenberg DA, 2007 A geometric method for automatic extraction of sulcal fundi. *IEEE transactions on medical imaging* 26 (4), 530–540. [PubMed: 17427740]
- Kao CY, Osher S, Qian J, 2004 Lax–friedrichs sweeping scheme for static hamilton–jacobi equations. *Journal of Computational Physics* 196 (1), 367–391.
- Kim SH, Lyu I, Fonov VS, Vachet C, Hazlett HC, Smith RG, Piven J, Dager SR, McKinstry RC, Pruett JR, et al., 2016 Development of cortical shape in the human brain from 6 to 24 months of age via a novel measure of shape complexity. *NeuroImage* 135, 163–176. [PubMed: 27150231]

- Knickmeyer RC, Gouttard S, Kang C, Evans D, Wilber K, Smith JK, Hamer RM, Lin W, Gerig G, Gilmore JH, 2008 A structural mri study of human brain development from birth to 2 years. *The Journal of Neuroscience* 28 (47), 12176–12182. [PubMed: 19020011]
- Knickmeyer RC, Xia K, Lu Z, Ahn M, Jha SC, Zou F, Zhu H, Styner M, Gilmore JH, 2016 Impact of demographic and obstetric factors on infant brain volumes: A population neuroscience study. *Cerebral Cortex*, 1–10. [PubMed: 25139941]
- Landman BA, Huang AJ, Gifford A, Vikram DS, Lim IAL, Farrell JA, Bogovic JA, Hua J, Chen M, Jarso S, et al., 2011 Multi-parametric neuroimaging reproducibility: a 3-t resource study. *Neuroimage* 54 (4), 2854–2866. [PubMed: 21094686]
- Lebed E, Jacova C, Wang L, Beg MF, 2013 Novel surface-smoothing based local gyrification index. *Medical Imaging, IEEE Transactions on* 32 (4), 660–669.
- Lee J, Kim SH, Oguz I, Styner M, 2016 Enhanced cortical thickness measurements for rodent brains via lagrangian-based rk4 streamline computation In: *SPIE Medical Imaging. International Society for Optics and Photonics*, pp. 97840B–97840B.
- Li G, Nie J, Wang L, Shi F, Gilmore JH, Lin W, Shen D, 2014a Measuring the dynamic longitudinal cortex development in infants by reconstruction of temporally consistent cortical surfaces. *Neuroimage* 90, 266–279. [PubMed: 24374075]
- Li G, Wang L, Shi F, Lyall AE, Lin W, Gilmore JH, Shen D, 2014b Mapping longitudinal development of local cortical gyrification in infants from birth to 2 years of age. *The Journal of Neuroscience* 34 (12), 4228–4238. [PubMed: 24647943]
- Looney CB, Smith JK, Merck LH, Wolfe HM, Chescheir NC, Hamer RM, Gilmore JH, 2007 Intracranial hemorrhage in asymptomatic neonates: prevalence on mr images and relationship to obstetric and neonatal risk factors 1. *Radiology* 242 (2), 535–541. [PubMed: 17179400]
- Luders E, Narr KL, Thompson PM, Rex DE, Jancke L, Steinmetz H, Toga AW, 2004 Gender differences in cortical complexity. *Nature neuroscience* 7 (8), 799–800. [PubMed: 15338563]
- Lui JH, Hansen DV, Kriegstein AR, 2011 Development and evolution of the human neocortex. *Cell* 146 (1), 18–36. [PubMed: 21729779]
- Lyu I, Kim S Styner M, 2015 Automatic sulcal curve extraction on the human cortical surface In: *Medical Imaging 2015: Image Processing. Vol. 9413 SPIE*, pp. 941324–1–941324–7.
- Lyu I, Kim SH, Bullins J, Gilmore JH, Styner MA, 2017 Novel local shape-adaptive gyrification index with application to brain development In: *International Conference on Medical Image Computing and Computer-Assisted Intervention. Springer*, pp. 31–39.
- Lyu I, Kim SH, Seong J-K, Yoo SW, Evans A, Shi Y, Sanchez M, Niethammer M, Styner MA, 2015 Robust estimation of group-wise cortical correspondence with an application to macaque and human neuroimaging studies. *Frontiers in neuroscience* 9.
- Lyu I, Kim SH, Seong J-K, Yoo SW, Evans AC, Shi Y, Sanchez M, Niethammer M, Styner MA, 2013 Group-wise cortical correspondence via sulcal curve-constrained entropy minimization In: *Information Processing in Medical Imaging. Springer Berlin Heidelberg*, pp. 364–375.
- Lyu I, Kim SH, Styner MA, 2016 Cortical surface shape assessment via sulcal/gyral curve-based gyrification index In: *2016 IEEE 13th International Symposium on Biomedical Imaging (ISBI). IEEE*, pp. 221–224.
- Meyer M, Desbrun M, Schröder P, Barr AH, 2003 Discrete differential-geometry operators for triangulated 2-manifolds In: *Visualization and mathematics III. Springer*, pp. 35–57.
- Moorhead TWJ, Harris JM, Stanfield AC, Job DE, Best JJ, Johnstone EC, Lawrie SM, 2006 Automated computation of the gyrification index in prefrontal lobes: methods and comparison with manual implementation. *Neuroimage* 31 (4), 1560–1566. [PubMed: 16600639]
- Ockendon JR, 2003 *Applied partial differential equations*. Oxford University Press on Demand.
- Osher S, Sethian JA, 1988 Fronts propagating with curvature-dependent speed: algorithms based on hamilton-jacobi formulations. *Journal of computational physics* 79 (1), 12–49.
- Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, Vogel AC, Laumann TO, Miezin FM, Schlaggar BL, Petersen SE, Nov. 2011 Functional Network Organization of the Human Brain. *Neuron* 72 (4), 665–678. [PubMed: 22099467]
- Qian J, Zhang Y-T, Zhao H-K, 2007 A fast sweeping method for static convex hamilton–jacobi equations. *Journal of Scientific Computing* 31 (1), 237–271.

- Ramer U, 1972 An iterative procedure for the polygonal approximation of plane curves. *Computer graphics and image processing* 1 (3), 244–256.
- Schaer M, Cuadra MB, Tamarit L, Lazeyras F, Eliez S, Thiran J, 2008 A surface-based approach to quantify local cortical gyrification. *Medical Imaging, IEEE Transactions on* 27 (2), 161–170.
- Schmitt JE, Watts K, Eliez S, Bellugi U, Galaburda AM, Reiss AL, 2002 Increased gyrification in williams syndrome: evidence using 3d mri methods. *Developmental medicine and child neurology* 44 (5), 292–295. [PubMed: 12033713]
- Sethian JA, 1996 A fast marching level set method for monotonically advancing fronts. *Proceedings of the National Academy of Sciences* 93 (4), 1591–1595.
- Sethian JA, Vladimirsky A, 2003 Ordered upwind methods for static hamilton–jacobi equations: Theory and algorithms. *SIAM Journal on Numerical Analysis* 41 (1), 325–363.
- Su S, White T, Schmidt M, Kao C-Y, Sapiro G, 2013 Geometric computation of human gyrification indexes from magnetic resonance images. *Human brain mapping* 34 (5), 1230–1244. [PubMed: 22331577]
- Toro R, Perron M, Pike B, Richer L, Veillette S, Pausova Z, Paus T, 2008 Brain size and folding of the human cerebral cortex. *Cerebral cortex* 18 (10), 2352–2357. [PubMed: 18267953]
- Tsitsiklis JN, 1995 Efficient algorithms for globally optimal trajectories. *IEEE Transactions on Automatic Control* 40 (9), 1528–1538.
- Van Essen DC, Drury HA, Dickson J, Harwell J, Hanlon D, Anderson CH, 2001 An integrated software suite for surface-based analyses of cerebral cortex. *Journal of the American Medical Informatics Association* 8 (5), 443–459. [PubMed: 11522765]
- Wig GS, Laumann TO, Petersen SE, 2014 An approach for parcellating human cortical areas using resting-state correlations. *Neuroimage* 93, 276–291. [PubMed: 23876247]
- Worsley K, Taylor JE, Carbonell F, Chung M, Duerden E, Bernhardt B, Lyttelton O, Boucher M, Evans A, 2009 Surfstat: A matlab toolbox for the statistical analysis of univariate and multivariate surface and volumetric data using linear mixed effects models and random field theory. *Neuroimage* 47, S102.
- Zaharescu A, Boyer E, Varanasi K, Horaud R, 2009 Surface feature detection and description with applications to mesh matching. In: *Computer Vision and Pattern Recognition, 2009. CVPR 2009. IEEE Conference on. IEEE*, pp. 373–380.
- Zilles K, Armstrong E, Moser KH, Schleicher A, Stephan H, 1989 Gyrification in the cerebral cortex of primates. *Brain, Behavior and Evolution* 34 (3), 143–150.
- Zilles K, Armstrong E, Schleicher A, Kretschmann H-J, 1988 The human pattern of gyrification in the cerebral cortex. *Anatomy and embryology* 179 (2), 173–179. [PubMed: 3232854]

Highlights

- A cortical shape-adaptive kernel is proposed to quantify cortical folding patterns.
- The proposed method captures cortical folding in a biologically relevant way.
- A novel local gyrification achieved a high reproducibility in multi-scan dataset.
- Novel refined positive and negative age associations were found on cortical regions.

Figure 1:

Different kernel shapes with the same area on the adult brain: (a) Euclidean sphere intersection, (b) equidistant geodesics on the surface, (c) the proposed cortical shape-adaptive kernel. As the kernel size increases, the conventional kernel shapes are likely to cover multi-sulcal (gyral) regions than the proposed kernel (the color indicates iso-contours).

Figure 2:

A schematic overview of the proposed pipeline. 1) The cortical surface is reconstructed from an MR image, and the outer hull is computed from the cortical surface. 2) Sulcal and gyral regions are segmented as sulcal and gyral curves. 3) The entire cortical regions are segmented by computing geodesic distance (equivalently, travel-time) between the sulcal and gyral regions. 4) A tensor field is estimated from the travel-time map at every location of the surface. 5) The cortical shape-adaptive kernel is created by performing the wavefront propagation over the tensor field.

Figure 3:

An overview of the tensor field computation. (a) Sulcal (*red*) and gyral (*blue*) curves are automatically extracted from the cortex for sulcal and gyral region segmentation. (b) For entire region segmentation, travel-time from the curves to every vertex is computed by solving the eikonal equation. (c) A gradient map of the travel-time map is obtained in the tangent space of the cortex. (d) The travel-time map is normalized to consistently capture cortical properties: sulcal fundus and gyral crown (*blue*) or sulcal bank (*red*).

Figure 4:

Two different types of synthetic normalized travel-time maps S on the plane and their kernel shapes with a constant area by varying η . The respective travel-time maps are obtained from the middle horizontal (*top*) and marginal horizontal (*bottom*) sources (*blue*). The kernel is created at the center of the map as a source point. The kernel is adaptively elongated faster as η becomes smaller (*top*), whereas the kernel remains as isotropic as possible even with a small value of η (*bottom*). From the second to fourth columns, the color indicates iso-contours over time.

Figure 5:

Kernels at an arbitrary example sulcal point on the same subject surface using different approaches with a fixed area on the outer hull $\rho = 316 \text{ mm}^2$. The disc kernel (intersection of the outer hull and the sphere) is obtained in FreeSurfer (*left*). The proposed kernel can be obtained with different regularization factors: isotropic ($\eta = 1.0$, *middle*) and anisotropic ($\eta = 0.5$, *right*) propagation. The color indicates iso-contours over time.

Figure 6:

The average local gyrification index on the Kirby dataset in the lateral and medial views. The sulcal folding patterns are well captured by the isotropic (*middle*) and anisotropic (*right*) kernels. The sulcal fundi and gyral crowns are more adaptively captured in the anisotropic kernel, whereas several folding patterns (e.g., precentral gyrus or superior temporal sulcus) are smoothed out in the isotropic kernel at proposed local size (*top*). Even with a large kernel, the folding patterns are better revealed by the anisotropic kernel than by that of FreeSurfer or the isotropic kernel (*bottom*). The inflated surface is used for better visualization. The area of 1,264 mm² corresponds to approximately a circle with a radius of 20 mm, which is a typical size of the kernel used in the FreeSurfer method.

Figure 7:

An example of the proposed gyrification index on an individual cortical surface using varying kernels sizes (a-d). Overall cortical folding patterns are captured in both small and large kernels. The local cortical folding patterns are better represented along sulci and gyri by the small kernel.

Figure 8:

Reproducibility of the conventional and proposed methods. The reproducibility is measured by coefficient of variation (CoV). Overall, the proposed kernel-based local gyrification index achieves a comparable or better reproducibility to the conventional method for both small and large kernel sizes. The isotropic kernel shows a higher reproducibility as its measurement is not influenced by curve extraction errors unlike the anisotropic kernel. The inflated surface is used for better visualization.

Figure 9:

The age effect on cortical gyrification. Most cortical regions have positive associations of cortical gyrification over ages (shown here t -value maps before (*left*) and after (*right*) correction ($q < 0.05$)). Deep sulcal regions such as central and cingulate sulci have negative associations.

Figure 10:

The sex effect (*red*: male, *blue*: female) on cortical gyrification with *t*-value maps before (*left*) and after (*right*) correction ($q < 0.05$). The female subjects show higher gyrification in the right superior temporal lobe, whereas the male subjects show higher development in primary motor.

Figure 11:

The gestational age effect at birth on cortical gyrification with t -value maps before (*left*) and after (*right*) correction ($q < 0.05$). Most cortical regions have positive associations of cortical gyrification over ages, whereas negative associations are shown in the primary motor cortex and collateral fissure.

Figure 12:

Comparison: the average local gyrification index using two different kernel sizes ((a) small kernel: 200 mm^2 ($r \approx 8 \text{ mm}$) and (b) large kernel: 800 mm^2 ($r \approx 16 \text{ mm}$) at age 2 years). The FreeSurfer method is unstable in large sulcal regions using the small kernel while the overall measurements are widely blurred with the large kernel. The isotropic and anisotropic propagation-based methods overall capture similar cortical folding patterns. The inflated surface is used for better visualization.

Figure 13:

Comparison: associations with demographic effects using large kernel size (800 mm^2 ($r \approx 16 \text{ mm}$) at age 2 years). The FreeSurfer method captures overall blurred measurements across the entire cortex, whereas the proposed method provides refined measurements in a more adaptive and detailed way along the sulcal folding. In addition, even with a large kernel size, the proposed gyrification index has similar patterns to that with the small kernel size (see

Fig. 9–11). Higher t -values of the developmental effects are observed in the anisotropic propagation than the isotropic propagation while their overall patterns are quite similar.

Table 1:

Average closest distance of the adaptive kernel in the multi-scan dataset (unit: *mm*). The proposed adaptive kernel achieves a high reliability (i.e., low distance measures) even for large kernels at high anisotropy in terms of triangulated size, given that the triangle edge length is 1.16 ± 0.46 *mm*.

Area	Radius	$\eta = 1.0$	$\eta = 0.5$	$\eta = 0.2$	$\eta = 0.1$
316 <i>mm</i> ²	10 <i>mm</i>	0.56 ± 0.19	0.65 ± 0.21	0.71 ± 0.23	0.73 ± 0.24
632 <i>mm</i> ²	14 <i>mm</i>	0.66 ± 0.22	0.78 ± 0.24	0.85 ± 0.26	0.88 ± 0.27
948 <i>mm</i> ²	17 <i>mm</i>	0.72 ± 0.23	0.85 ± 0.26	0.94 ± 0.28	0.97 ± 0.29
1,264 <i>mm</i> ²	20 <i>mm</i>	0.76 ± 0.24	0.91 ± 0.26	1.01 ± 0.29	1.04 ± 0.30

Table 2:

Coefficient of variation of the local gyrification index in the multi-scan dataset (unit: %). Overall, the proposed method achieves a higher reliability than the conventional method. The proposed local gyrification index exhibits a slightly lower (but still comparable) reproducibility for highly anisotropic kernels ($\eta = 0.1$) due to expected variability and errors in the sulcal and gyral curve extraction.

Area	Radius	FreeSurfer	$\eta = 1.0$	$\eta = 0.5$	$\eta = 0.2$	$\eta = 0.1$
316 mm^2	10 mm	7.17 ± 7.84	3.64 ± 1.57	4.16 ± 1.49	4.78 ± 1.60	5.21 ± 1.79
632 mm^2	14 mm	4.87 ± 2.12	2.67 ± 1.05	3.18 ± 1.04	3.74 ± 1.17	4.13 ± 1.38
948 mm^2	17 mm	3.93 ± 1.65	2.31 ± 0.89	2.76 ± 0.88	3.26 ± 1.00	3.61 ± 1.19
1,264 mm^2	20 mm	3.11 ± 1.29	2.13 ± 0.79	2.52 ± 0.80	2.96 ± 0.92	3.28 ± 1.09

Table 3:

Population statistics of the Early brain development studies (EBDS) dataset used in this study.

Scans	Total number	Male	Female	Age (days)	Age range (days)	Gestational age (days)
Neonate	178	88	90	20.89 ± 9.50	6–68	275.27 ± 11.29
1 year	85	44	41	385.27 ± 22.84	343–481	273.36 ± 11.86
2 years	76	44	32	746.54 ± 25.03	693–827	272.62 ± 14.04
Total	339	176	163	-	-	274.20 ± 12.12