Research Article • DOI: 10.2478/s13380-014-0202-1 • Translational Neuroscience • 5(1) • 2014 • 17-24

Translational Neuroscience

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Springer

CORTICAL SURFACE COMPLEXITY IN A POPULATION-BASED NORMATIVE SAMPLE

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Abstract

MRI studies on abnormal brain development are dependent on the quality, quantity, and type of normative development data available for comparison. Limitations affecting previous studies on normative development include small sample sizes, lack of demographic representation, heterogeneous subject populations, and inadequate longitudinal data. The National Institutes of Health Pediatric MRI Data Repository (NIHPD) for normative development was designed to address the aforementioned issues in reliability measures of control subjects for comparison studies. The subjects were recruited from six Pediatric Study Centers nationwide to create the largest, non-biased, longitudinal database of the developing brain. Using the NIHPD, we applied a 3D shape analysis method involving spherical harmonics to identify the cortical surface complexity of 396 subjects (210 female; 186 male) between the ages of 4.8 y and 22.3 y. MRI data had been obtained at one, two, or three time points approximately two years apart. A total of 144 participants (79 female; 65 male) provided MRI data from all time points. Our results confirm a direct correlation between cortical complexity and age in both males and females. Additionally, within the examined age range, females displayed consistently and significantly greater cortical complexity than males. Findings suggest that the underlying neural circuitry within male and female brains is different, possibly explaining observations of sexual dimorphism in social interaction, communication, and higher cognitive processes.

Keywords

• Brain/growth & development • Cerebral cortex • Spherical harmonics

Received 17 January 2014
accepted 13 February 2014

Introduction

Variability in global and regional cortical development exists even amongst healthy control subjects. This lends to the importance of ascertaining normative measurements of brain development from a longitudinal database stemming from a large, demographically balanced population [1]. Presently, the National Institutes of Health Pediatric MRI Data Repository (NIHPD) is the largest non-biased, multi-center, longitudinal sample of healthy control subjects available providing the most reliable data for normative measurements of specific brain regions and growth patterns during development. The purpose of this study was to identify confidence intervals of normative pediatric cortical shape complexity, which is defined as a measure that quantifies the spatial frequency of gyrification and fissuration of the brain surface [2]. To do this, we applied a method of 3D shape analysis called spherical harmonics to MRI data from 396 subjects (210 female; 186 male) aged 4.8 to 22.3 years of age.

Spherical harmonics overcome the limitations of spatial normalization and volume measurements by investigating differences in shape complexity among brains. Spherical harmonics (SH) are functions arising in physics and mathematics when spherical polar coordinates are used in investigating physical problems in three dimensions [3]. They form an orthogonal basis for functions defined on the unit sphere, analogous to the Fourier basis of sines and cosines for functions defined on a circular domain. The SPHARM algorithm [4] uses spherical harmonics to decompose any genus zero surface into its frequency components. Spatial normalization systems are commonly used to reference a given brain in which individual subject data is superimposed on the atlas data [5,6]. However, a major disadvantage of superimposing individual brain images onto a standard atlas is that much of the variability of the individual brain is stripped away as each brain is contorted to match the template atlas. Instead of matching each brain to a standard atlas, spherical harmonics reconstruct a 3D cortical surface mesh model to match each individual brain, providing an individualized measure of shape complexity for each subject.

In an attempt to identify normal brain variation with age and gender, the Brain Development Cooperative Group [7] established a normative reference of cortical volume during development using the subjects from the NIHPD. However, measurements of cortical volume can be misleading in that two brains could have the same amount of cortical white matter and gray matter volume, but be distributed differently throughout the brain. Additionally, automated differentiation of tissue lack anatomical specificity and may vary depending on the clarity and quality of MRI data, diminishing the reliability of reproducibility of volume measurements [8]. The use of spherical harmonics overcomes these limitations by measuring the shape of

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the cortex rather than its volume, including the dynamics of both gyri and sulci.

Spherical harmonics are combinations of basic mathematical functions defined on the unit sphere. The spherical harmonic shape analysis consists of a Fourier transform, which is used as a mathematical operation described as a function of polar angle θ and azimuthal angle φ that decomposes a function into frequency components [9]:

$$f(\theta,\varphi)=\sum_{l=0}^{\infty}\sum_{m=-l}^{l}b_{lm}Y_l^m(\theta,\varphi)$$

Spherical harmonics are preferred over other techniques such as hyperquadrics and superquadrics because they (1) require only a few homologous landmarks to register objects needed to execute the analysis and (2) allow for heterogeneous shapes of 3D biological structures to be ordinated in order to provide a developmental change in shape with time [10]. Brain volume is normalized as each brain is mapped to a single unit sphere, which by definition has a radius of 1.

Experimental procedures

Subjects

Data collection for the NIH Pediatric Data Repository (NIHPD) took place between November 2001 and November 2007 at six Pediatric Study Centers across the United States making this the largest, non-bias, multi-center, longitudinal study of normative development presently available [11]. Participants of the NIHPD study provided MRI data at one, two or three different time points within approximately two year intervals. Data for the NIHPD study is actually broken into two age groups. *Objective 1* includes individuals aged 4.6–18.3 years at the first MRI visit and *Objective 2* includes individuals aged 7 days to 4.5 years at the first MRI visit [11]. For purposes of our study, we used data from *Objective 1* which had 396 MRIs (219 females; 186 males) that were suitable for our methods and included individuals as young as 4.8 years of age at the time of the MRI first visit and as old as 22.3 years of age at the time of the third MRI visit.

Magnetic resonance imaging

MRIs were obtained using either a General Electric or Siemens Medical Systems 1.5 Tesla MRI scanner. Data processing was performed at the Spectroscopy Processing Center (SPC) at UCLA. For purposes of this study, we used the T1-weighted image data. Each MRI data set is 256 x 256 x 180 matrix and each scan consists of 180 contiguous 1.5 mm thick slices in the axial plane from the top of the head to the bottom of the neck.

Image analysis

Release 4.0 of the NIHPD was made available on June 26, 2010 and includes a labeled matrix of stereotaxic space and age-specific MRI atlas templates for each brain. Image segmentation was completed by the NIH for both *Objective 1* and *Objective 2,* albeit, only *Objective 1* data was used in this study. The T1 weighted imaging data was transferred onto a Dell Precision workstation with two quad-core Xeon processors and 24 GiB RAM per processor, running the latest version of Matlab (MathWorks, Natick, MA, USA) for image processing and analysis.

Spherical harmonics

The first step is to reparameterize the surface for reconstruction which is done by mapping a surface mesh around the image using an automated, non-biased point by point coordinate system. We accomplished this task using the Attraction-Repulsion Algorithm as previously published [12]. After finding a spherical parameterization through conformational mapping of the surface, a spherical harmonic transform is applied to each coordinate function of the original surface mesh. There are 40,962 points used to create a spherical harmonic mesh. The resulting spherical harmonic coefficients contain information about the spatial frequency components of the analyzed brain surface. The error that is calculated between the unit sphere and the actual image provides the means to analyze morphometric changes in cortical growth. A common processing step for cortical surfaces is to map the cortical surface mesh to a spherical surface for improved brain registration and advanced analytical techniques. The ideal spherical mapping is isometric with all angles and areas preserved, which would potentially improve the quality of subsequent processing steps. However, this also leads to distortions when mapping angles of the cortical surface to a sphere. To overcome this dilemma, our lab has developed a analysis framework (Figure 1) to generate a pseudo-isometric spherical mapping of the cortical surface. To begin with, we used an algorithm that is based on the CGAL library to generate a triangulated 3D mesh in order to approximate the cortical surface [13]. The initial spherical map is a conformal map produced through the Laplace-Beltrami operator equation optimized with a Möbius transformation. The conformal map is then post-processed using a processing pipeline consisting of novel algorithms designed to reduce area distortion. Therefore, the spherical maps generated using our methods have minimal distortions in area and angle. As previously published, our Analysis Framework Model includes the following steps [12]:

1. 3D cortical segmentation, with a deformable 3D boundary, controlled by two probabilistic visual appearance models (the learned prior and the estimated current appearance one)
2. Construction of a triangular mesh *M* of the cortical surface
3. Spherical parameterization of the surface mesh
4. Representation of *M* as a SPHARM model
5. Computation of the shape complexity *S*

Spherical deformation

From the original mesh, we used the Laplacian filtering equation to smooth the desired surface. We then used the Attraction-Repulsion Algorithm to deform the mesh into a unit sphere:

$$M=\{(x,y,z)\,|\,x=X(\theta,\varphi);\,y=Y(\theta,\varphi);\,z=Z(\theta,\varphi)\}$$

The Attraction-Repulsion mapping approach requires all the mesh nodes to meet two conditions: (i) the unit distance of each node from the center of the cortex, and (ii) an equal distance of each node from all of its nearest neighbors [12]. Using spherical harmonics, we reconstructed estimates of the original cortex using a smoothing constant of 10^{-5}.

The SPHARM method [4] constructs a SH representation of *M* by expanding each of *X*, *Y*, and *Z* as an SH series. Then we can define the

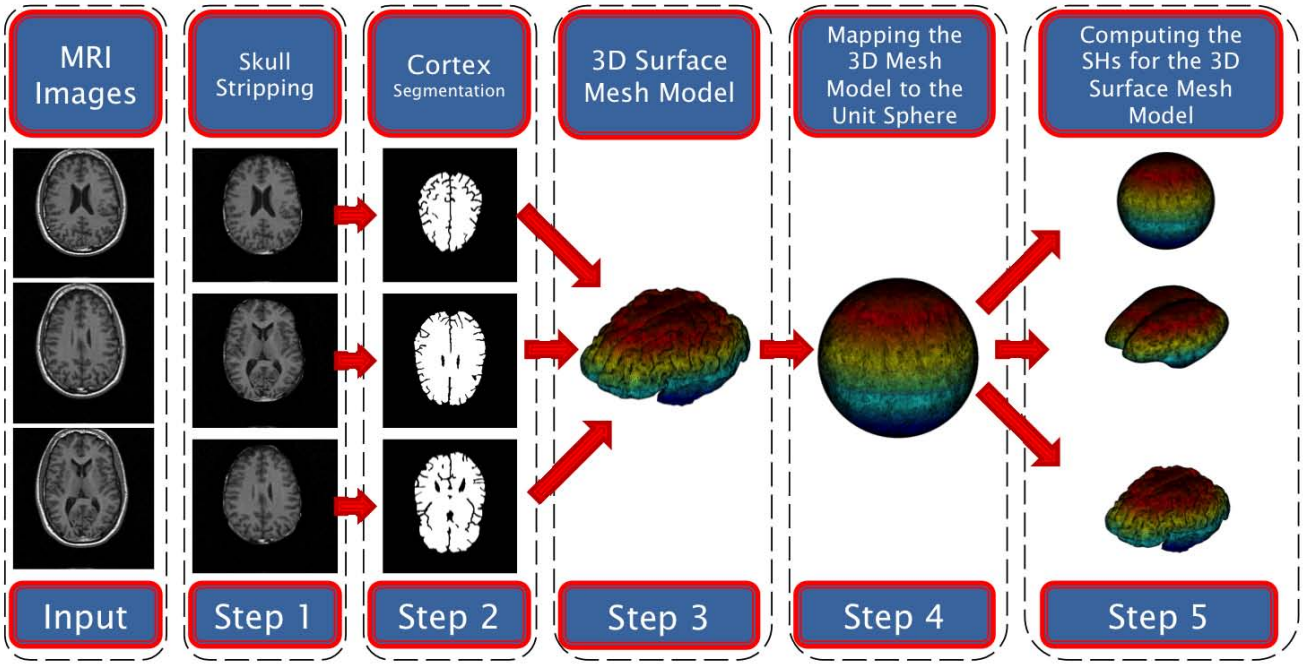

Figure 1. Spherical harmonics shape analysis [12].

surface complexity of *M* as the combined high frequency content of its SH components,

$$S(M)=\frac{S(X)+S(Y)+S(Z)}{\|X\|^2+\|Y\|^2+\|Z\|^2}.$$

Each *S*(*f*) (*f* = *X*, *Y*, or *Z*) is defined as the sum of the squared truncation error when using an *L* + 1 order SH series:

$$S(f)=\left\|f-f_L\right\|^2=\left\|\sum_{l=L+1}^{\infty}\sum_{m=-l}^{l}b_{lm}Y_l^m\right\|^2=\sum_{l=L+1}^{\infty}\sum_{m=-l}^{l}\left|b_{lm}\right|^2$$

The normalization factor in the denominator of *S*(*M*) ensures that the surface complexity is independent of brain volume; i.e. it is a measure of shape rather than size.

Results

To investigate measurements of cortical complexity, accurate automated segmentation was performed using a conventional 3D parametric deformable boundary. Once a 3D cortical surface mesh was constructed using the standard number of 40,962 vertices and 81,920 triangle elements (polygons) per hemisphere [14,15], spherical deformation took place following an in-house 5-step analysis framework model. Evolution was controlled using two probabilistic visual appearance models:

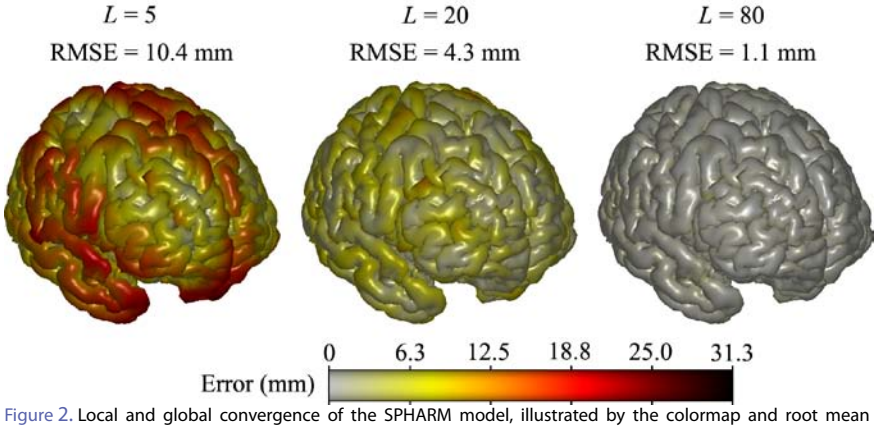

Figure 2. Local and global convergence of the SPHARM model, illustrated by the colormap and root mean squared error (RMSE), respectively. The model order is *L* + 1, i.e. *L* the maximum degree of the truncated SH series for *X*, *Y*, and *Z*.

1st Order Appearance Model: A linear combination of discrete gaussians (LCDG) allowed classification of gray-scale pixels as white matter (WM), gray matter (GM), or cerebral spinal fluid (CSF) by creating a rough segmentation of the cortex.

2nd Order Appearance Model: A 3D Markov-Gibbs random field (MGRF) model of the pixel intensities with translation and rotation-invariant pairwise voxel interaction allowed the detection of edges, which created a fine segmentation by removing gaps and correcting incorrect labels of GM, WM, CSF, etc.

The brain is modeled with a translation and rotation invariant generic MGRF with voxel-wise and central-symmetric pair-wise voxel interaction specified by a set *N* of characteristic, central symmetric neighborhoods [16]. In our case, *N* was the set of voxels within the neighborhood of 3 to 5 mm. Set *N* was measured by the Manhattan distance to avoid square and square root operations as seen in the Euclidean distance that requires longer processing time. Once each voxel was clearly identified, automated cortical segmentation took place next [12].

The complete data set (Figure 3, Figure 4) includes 396 individuals (210 females; 186 males) aged 4.8 years to 22.3 years (mean 12.3 years) with useful MRI data from at least one visit. Of these, 144 (79 females; 65 males) had MRI data from three visits. Within the three-visit subset, age at visit #2 ranged from 6.5 years to 20.3 years (mean 12.8 years).

Surface complexity

Surface complexity was modeled as a polynomial in age with sex-dependent intercept and slopes, and also a random intercept for each individual to account for repeated measures. The polynomial degree, *k*, was selected from the set {1, ..., 10} in order to minimize the Akaike information criterion.

The optimal degree of the polynomial in age was $k = 2$ (Figure 5). The effects of age ($F_{2,443} = 205.4$; $p = 0.0001$) and sex ($F_{1,394} = 206.3$; $p = 0.0001$) were both statistically significant, although the age dependence did not significantly differ between male and female ($F_{2,443} = 0.926$; $p = 0.397$). The fitted models were:

$$S = \begin{cases} 1.0251 + 7.425\times10^{-4}t + 5.786\times10^{-5}t^2 & \text{(Male)} \\ 1.0452 + 6.169\times10^{-4}t + 7.497\times10^{-5}t^2 & \text{(Female)} \end{cases}$$

Instantaneous rate of change in S

Rate of change in surface complexity *S* was estimated by finite differencing:

$$\frac{dS}{dt} = \frac{S_{\text{visit \#3}} - S_{\text{visit \#1}}}{t_{\text{visit \#3}} - t_{\text{visit \#1}}}$$

A plot of *dS/dt* versus $t_{\text{visit \#2}}$ revealed an upward trend with an asymmetric distribution of observations about the mean. Statistical analysis employed a generalized linear model with gamma-distributed responses. The independent variables were age, sex, and their interaction term. The best fit model was:

$$\frac{dS}{dt} = \begin{cases} (574 - 17.15t)^{-1} & \text{(Male)} \\ (481 - 13.16t)^{-1} & \text{(Female)} \end{cases}$$

The effect of sex and the age*sex interaction were insignificant ($t_{140} = -0.627$; $p = 0.532$ and $t_{140} = 0.396$; $p = 0.693$, respectively). The effect of age alone was statistically significant ($t_{140} = -3.01$; $p = 0.003$) demonstrating that

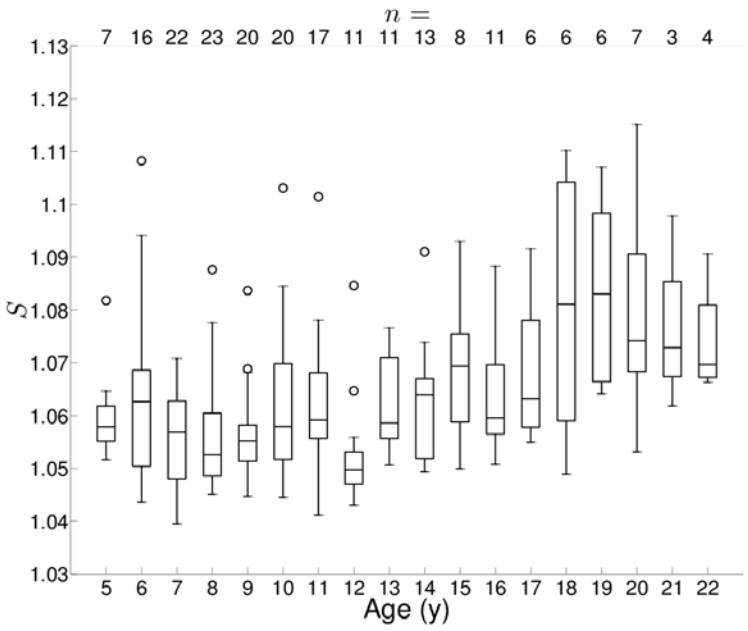

Figure 3. Box plot of cortical surface complexity in the female subset. Age is binned by year; the number of participants per bin is indicated above the axes.

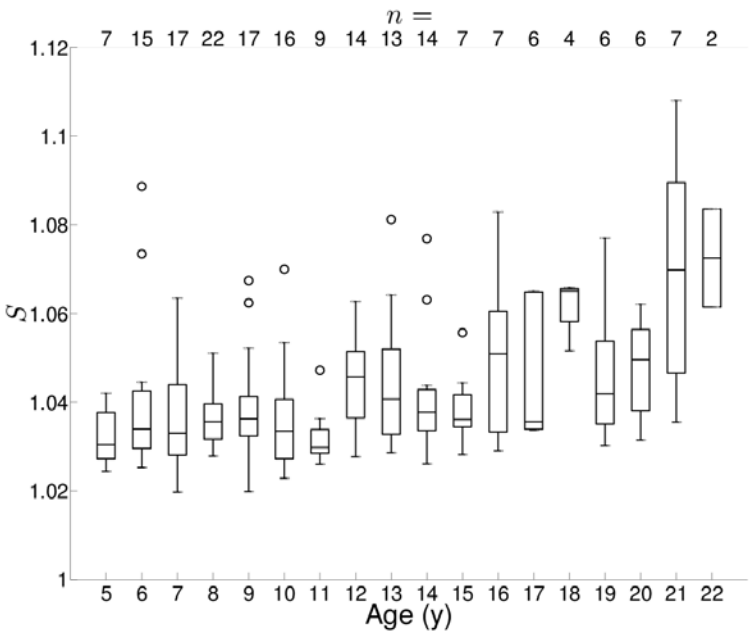

Figure 4. Box plot of cortical surface complexity in the male subset. Results for all 396 subjects are the same as our one-to-one age matched comparison between genders, indicating that cortical complexity increases with age in both genders, but that cortical complexity is consistently and significantly greater in females than males between the ages of 4.8 and 22.3.

shape complexity increased with age in both genders (Figure 6). All *p*-values are two-sided. Ignoring the insignificant sex-dependent terms, the best fit was:

$$\frac{dS}{dt} = (527 - 15.15t)^{-1}$$

Variability of *S* within age brackets

Age was binned into three categories: < 10 years, 10–15 years, and > 15 years. Mean *S* was computed for male and female in each of these ranges, weighting the data by the reciprocal of the number of visits so that all individuals contributed equally to the results. The standard deviation of the weighted mean was also computed. The Levene's test does not rule out that the standard deviation of S is the same for male and female within each age bracket: $F_{1,277}$ = 0.0195, p = 0.889 (< 10 years); $F_{1,333}$ = 1.62, p = 0.204 (10–15 years); $F_{1,227}$ = 1.36, p = 0.245 (> 15 years).

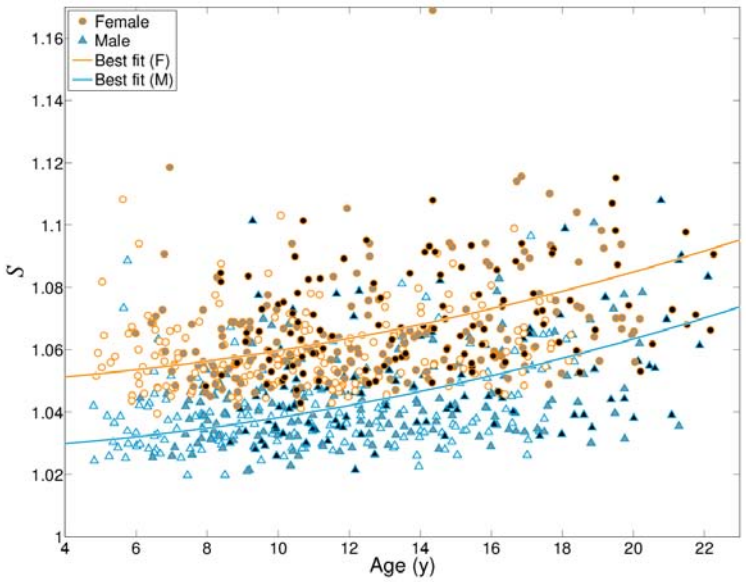

Figure 5. Cortical surface complexity for all 396 subjects in relation to age at each MRI visit along with the fitted mixed-effects linear model, quadratic in age.

Discussion

During development, as the brain is encased within a nonmalleable skull, it is not able to expand its cortical surface area; therefore, it must fold within itself creating grooves and ridges in a process known as gyrification. The topography of the cortical surface area becomes more convoluted throughout prenatal and early postnatal development [17]. Early postmortem findings have shown that normal brain maturation occurs from inferior to superior and from posterior to anterior structures [18,19]. Early neuroimaging studies confirmed that the brainstem, cerebellum, sensorimotor cortex and thalamus develop early within the infant brain, followed later by development of the association cortices of the frontal, temporal, parietal and occipital lobes [18,19]. Evidence of this order of maturation is consistent with outward developmental stages of infant behaviors [20]. Neuroimaging studies that provide a quantitative morphological assessment of individual brain structures based on volumetric measurements have been extremely resourceful in identifying increases and decreases in gray matter and white matter volume with age or illness as seen in Alzheimer's disease or multiple sclerosis. However, volumetric changes do not necessarily reflect structural changes in cortical development such as bending, flattening, thickening, or thinning of specific gyri or subcortical structures within the brain. Gerig and colleagues [21] were the first to address this issue by implementing 3D shape analysis methods using spherical harmonics or SPHARM. SPHARM is a unique method of congruency shape analysis that removes many of the standard parameters of variability in an object. It is also hierarchical in nature in

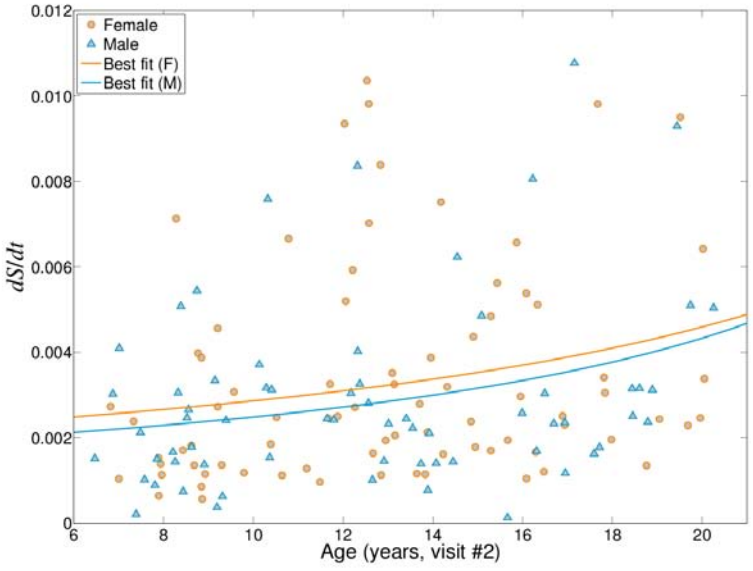

Figure 6. Rate of change in surface complexity *S* estimated by finite differencing at visit 2 in all the subjects who provided MRI data for a total of 3 visits.

that any shape can be parameterized by a set of basic functions, and these basic functions are then referred to as spherical harmonics. There is a high degree of variability among brains, which is in large part why spherical harmonics are an exceptional choice for mapping changes in cortical complexity. A primary challenge that occurs when examining shapes is the registration and positioning of the examined object. However, spherical harmonics actually remove the variability of these parameters by considering 3D surface data as a linear combination of specific basic functions and instead provide a rotation invariant common coordinate system in which shapes can be analyzed [4,21]. Spherical harmonics convert a 3D object into a unit sphere by decomposing the object of the orientation information that primarily accompanies its 3D shape representation. The unit sphere is a shape descriptor that is both descriptive and invariant to orientation where points are equally spaced from one another and sit at a distance of 1 from the center of the sphere. In regards to brain normalization, all brains are normalized during the decomposition phases so that even though male brains are anatomically larger than female brains, the unit sphere is proportionate to the overall brain size of each individual subject; hence, brain size does not influence variability. To further solidify that point, when it comes to 2D objects, size, rotation, twisting, warping, etc., these are all properties of shape transformations. The uniqueness of spherical harmonics is that this technique removes all properties of transformation by default. Therefore, if all transformations are effectively removed, scaling is also removed, and shape size becomes irrelevant. Because all of the analysis is based on this sphere, the brains are all normalized through this process. The brains are not altered prior to the unit sphere representation.

Results showed that both males and females exhibited a pattern of increased cortical shape complexity with age. According to our methods, the more complex the original shape is the more spherical harmonics are needed to recreate it. As such, a higher degree of error would indicate that more spherical harmonics were needed to reconstruct the mesh to match it to the original cortex. Keeping in mind that spherical harmonics methods normalize brain size by decomposing all brains down to a unit sphere, our methods required a higher degree of spherical harmonics to recreate the female cortex in comparison to the male cortex resulting in a consistently and significantly greater cortical surface complexity in females than in males between ages 4.6 to 22.3. Lastly, rate of change in cortical surface complexity within a group of subjects of the same age indicated that cortical growth follows a specific pattern of development. This pattern is likely to be consistent with outward observations of cognitive function involving higher order thinking and processing, which are likely to parallel Piaget's stages of cognitive development and hormonal changes in maturation.

Other studies that have investigated the cortical surface area have reported that male brains have greater cortical surface area than female brains when measured in their native space [22-24], but when area measurements were normalized by volume, females actually had more surface area than males [23], though not significantly. However, an investigation of cortical surface area did show highly significant sex differences after image scaling [24]. Two other studies also provided evidence for direct sex effects of cortical complexity in which the female brain revealed greater cortical complexity compared to males [2,24]. Luders *et al.* [2] estimated cortical complexity in the superior frontal, inferior frontal, temporal, parietal, and occipital lobar regions and found that female brains were more complex in the frontal and parietal lobes compared to males [2]. In a later study, Luders *et al.* (2006) used the mean curvature to quantify cortical convolution at multiple surface points, confirming findings of greater cortical surface complexity in the frontal and parietal lobes of females compared to males. Another study that estimated cortical complexity used a spatial resolution and regression model [25] and found significant sex-by-age interaction in children and adolescents for frontal brain regions with cortical complexity only increasing with age in females [26].

Cortical changes in myelination and synaptic regression are regionally specific reflecting a similar pattern to the outward developmental and behavioral changes observed throughout childhood and adolescence. Gray matter development follows a nonlinear prepubertal increase and postpubertal decrease [27]. Cortical gray matter development reflects a functional maturation sequence, in which the primary sensorimotor cortices and the frontal and occipital poles develop first, with the rest of the cortex catching up in a parietal-to-frontal (caudal-to-rostral) direction [27]. The course in which the cerebrum matured is consistent with relevant milestones in cognitive and functional development [27]. Higher-order association areas, such as the inferior temporal cortex, parts of the superior temporal gyrus, posterior parietal cortex, and prefrontal cortex, mature after lower-order association areas have developed [27]. Changes in cortical thickness relate to cognitive changes in normally developing children and adolescence [28]. It is thought that perhaps the loss of gray matter is due to synaptic pruning and possible changes in trophic glial and vasculature and/or even cell shrinkage [27].

MRI findings have shown that regional total lobar volumes highly correlate with total brain volume during development [29]. In regards to significant age effects, females were observed to have an increased amount of white matter significantly greater than any change in gray matter between 7 and 15 years of age, with the ratio of total gray matter volume to total white matter volume at 8% to 19%, respectively [29]. The significant change in female brain development between the ages of 7 and 15 is likely due in part to hormonal influences associated with menarche [30].

Conclusions

Our results indicate a direct relationship between an increase in age and an increase in gyrification during the age range examined. Both males and females exhibit a pattern of increased cortical complexity with age. However, cortical complexity is consistently and significantly greater in females than in males with age. As cortical complexity increases

with age, the rate of change in cortical surface complexity also increases. Rate of change in cortical complexity within a group of subjects of the same age indicates that cortical growth follows a specific pattern of development. This pattern is likely to be consistent with outward observations of cognitive function involving higher order thinking and processing. Previous research has also shown that males have approximately 10% more mean total cortical gray matter volume than females [1,31-33], which is often attributed to males having an overall larger brain than females. A larger skull would have more room for cortical growth to cover a larger surface area, whereas a smaller skull would have less room for cortical growth and instead of spreading out over a large surface area would become more compact by folding more deeply within itself over a smaller surface area. Deeper and more compact folding of the brain could explain why females have a greater cortical complexity than males. It might also suggest that female brains have closer connections between adjacent brain regions that might explain why females tend to perform better at multitasking than males. However, in considering the latent effects of fetal testosterone on local gray matter volume development, it is also possible that the cortical complexity of the male brain may eventually catch up to the female brain because fetal testosterone acts as a proximate signal in early development that triggers early cell processes that are not expressed until later in life [34].

This study also showed that 3D cortical shape analysis using spherical harmonics is able to accurately discriminate changes in cortical growth with age. As the complexity of cortical folding increases, the number of SHs needed to provide an accurate approximation of the shape also increases, so the greater the area under the curve, the greater the number of SHs were needed to fit the shape. The results of this study demonstrate differential patterns of brain maturation by age and gender that can be used as a reference for normative brain development. Early studies in childhood brain development have reported that brain volume growth follows an inverted U-shaped trajectory that peaks earlier in girls—around 10.5 years, compared to 14.5 years of age in boys [31-33,35]. In our study, the level of cortical complexity in a female at age 8 is roughly equivalent to the cortical complexity in a male at age 18.

Limitations of this study include the age range of subjects whose cortical complexity was analyzed. This study did not investigate cortical surface shape complexity of individuals enrolled in *Objective 2*, which included subjects aged newborn to 4.5 due to the vastly different MRI acquisition protocol that was implemented for infants. Additionally, the NIH MRI Pediatric Data Repository does not include individuals over the age of 22.3; therefore, we were unable to empirically determine whether this trend in greater cortical shape complexity exists from newborn beyond the second decade of life. However, the normative measurements of cortical surface shape complexity obtained from the NIHPD in this study could potentially be used in conjunction with brain volume measurements collected from the Brain Development Cooperative Group [11] as a diagnostic reference tool for identifying signs of delayed or abnormal brain development.

Acknowledgements

This research was supported by National Institutes of Health grants R01 MH-86784 and R01 HD-65279, and by a Wallace H. Coulter Translational Research Partnership Award.

Data used in the preparation of this publication were obtained from the NIH Pediatric MRI Data Repository created by the NIH MRI Study of Normal Brain Development. A listing of the participating sites and study investigators can be found online (http://www.pediatricmri.nih.gov/nihpd/info/participating_centers.html). This publication reflects the views of the authors and may not reflect the opinions or views of the Brain Development Cooperative Group Investigators or the NIH.

The authors declare no conflict of interest.

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