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A Deformation-based Approach for Characterizing Brain Asymmetries at Different Spatial Scales of Resolution

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Abstract

Background.—Structural cerebral asymmetries are hypothesized to provide an architectural foundation for functional asymmetries and behavioral lateralities. Studies of structural asymmetries typically focus on gray matter measures that are influenced by gross deformation fields used for normalization, and thus characterize a combination of different morphologic influences on structural asymmetries.

New Method.—A deformation-based morphometry approach was developed to characterize structural asymmetries at different spatial scales of resolution, which can provide relatively more specific inference about the morphologic reason(s) for structural asymmetries, using a dataset of 347 typically developing children (7.00 – 12.92 years).

Results.—Significant structural asymmetries were observed for a larger lobar spatial scale (e.g., frontal petalia) and for a smaller gyral/sulcal spatial scale of resolution (e.g., marginal sulcus). Total intracranial volume was significantly associated with asymmetries at the larger spatial scale of normalization, while age was significantly associated with asymmetries at the smaller scale of normalization. There were no significant anti- or fluctuating asymmetry effects based on Hartigan Dip Tests and Bonnett Tests, respectively.

Comparison with Existing Method(s).—While spatially similar asymmetries were observed in both gray matter and deformation field data (e.g., medial planum temporale / Heschl's gyrus), the deformation approach characterizes asymmetries based on three iterations of successively smaller scales of normalization.

Conclusions.—Structural asymmetries can be identified in normalization deformations with a procedure that is tailored for sensitivity to structures at different spatial scales of resolution where there may be different mechanisms for the expression of asymmetry.

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Keywords

Structural Asymmetries; Deformation-based Asymmetry; Directional Asymmetries; Jacobian Determinant

1. Introduction

The functional significance of hemispheric asymmetries in brain structure remains an intriguing and largely unexplained characteristic of brain organization (Güntürkün & Ocklenburg 2017; Hugdahl & Davidson, 2004; Toga & Thompson 2003). Frontal and occipital petalia, leftward planum temporale asymmetry, rightward superior temporal sulcus asymmetry, and leftward anterior insula asymmetries are consistently observed in voxel-based morphometry gray matter asymmetry analyses across pediatric (Eckert et al., 2008) and adult samples (Good et al., 2001; Watkins et al., 2001), for example. These and other structural asymmetries are widely thought to explain functional asymmetries (e.g., Craig, 2005). Functional differences in the extent of activity between homologous brain regions (Conant et al., 2014; Shulman et al., 2010) may reflect hemispheric differences in the spatial extent of canonical functional networks (Agcaoglu et al., 2015), and perhaps functional connectivity within each hemisphere (Raemaekers et al., 2018). While there is some evidence to support the premise that structural asymmetries relate to functional asymmetries and behavioral lateralization (Biduła & Króliczak, 2015; Chiarello et al., 2013; Keller et al., 2018; Josse et al. 2009), significant structure-function asymmetries are not always observed (e.g., Eckert et al., 2006; Specht & Wigglesworth, 2018), perhaps due to the sensitivity of structural asymmetry methods to gross morphologic relative to finer scale asymmetries.

Gray matter asymmetries are often reported based on data that has been modulated or adjusted for volumetric displacement of tissue during normalization to a template image and can thus reflect multiple sources of independent anatomical variance (Bruner & Ogihara, 2017). Displacement or deformation information can be analyzed separately from the gray matter data (Ashburner et al., 1998) and can be characterized across the brain to include white matter regions that may influence modulated gray matter results. Moreover, deformations can be examined across different spatial scales to characterize the spatial resolution of an asymmetry and increase measurement sensitivity. Here we describe a deformation-based method for identifying structural asymmetries at different spatial scales of resolution and determines the extent to which unique asymmetry patterns exist for different spatial scales (i.e., lobar to sulcal/gyral).

Voxel-based structural asymmetries that are typically reported in the neuroimaging literature can be considered directional asymmetries. That is, a consistent left or right asymmetry is observed across a sample (Palmer and Strobeck, 1986; Atkinson et al., 2016). Body morphology also exhibits fluctuating asymmetries. That is, there is no consistent asymmetry direction and these individual-level asymmetries have been hypothesized to provide behavioral advantages (Vallortigara & Rogers, 2005) or reflect developmental instability in morphologic development (Thoma et al., 2002). Fluctuating asymmetries have a platykurtic distribution and can be characterized by measuring the kurtosis of the distribution (Palmer

and Strobeck, 1986; Van Dongen, 2018). In the current study, kurtosis estimates were used to define fluctuating asymmetries. Fluctuating asymmetries were predicted to occur in more lateral cortical regions where there is gyral/sulcal variability and for finer scale deformation parameters compared to subcortical regions that exhibit less morphological variability.

2. Materials and Methods

2.1 Participants.

T1-weighted images from 347 typically developing children without evidence of reading or cognitive impairments were included in this study (49% female; average age = 9.69, sd = 1.70, 7.00 – 12.92 years; right-handed for writing or Edinburgh handedness questionnaire > 10 or had been classified as right-handed) and contributed from eight research sites (Southern Illinois University = 76; University of California San Francisco = 37; University of Washington = 34; Georgetown University = 33; Vanderbilt University = 47; Stanford University = 38; Yale University / Haskins Laboratories = 72; University of Alberta = 10) for a retrospective multi-site study with Institutional Review Board (IRB) approvals to share data that were collected with procedures guided by the Declaration of Helsinki. Medical University of South Carolina IRB approval was also obtained to receive de-identified data.

2.2 Deformation-Based Asymmetry Image Processing.

The native space and skull-stripped T1-weighted images were denoised (Manjon et al., 2010), rigidly aligned to the MNI template, and segmented using SPM12 for the gray matter analyses described below and to obtain a measure of total intracranial volume (TICV) based on the summed voxel probabilities across gray matter, white matter, and CSF images. Each rigidly aligned native space image was then left-right flipped using the SPM12 reorient utility. Together, the original and left-right flipped images made it possible to create a study-specific symmetrical template using diffeomorphic normalization with the ANTS Greedy SyN approach (ANTS v2.0; <http://stnava.github.io/ANTs/>; Avants et al., 2011). This first normalization procedure was performed using ten warping iterations or steps [Normalization parameters steps 1-10: Cross-correlation metric (mm radius = 4.00); SyN (2, 1, 1); Gaussian regularization (4.00); steps (Step 1: 30×90×20×12; Steps 2-10: 30×90×30×20)]. The average image from each normalization step served as the target for each subsequent normalization. Here the goal was to create a template image that best represented the average anatomical space of the sample.

A second normalization procedure was then performed that focused on characterizing individual differences in brain morphology at three different spatial scales of resolution using the study-specific template described above as the target. Three normalization steps of larger to smaller scale resolution were used to warp the rigidly-aligned native space T1-weighted images to the study-specific symmetrical template described earlier [Normalization parameters: Cross-correlation metric (mm radius = Step 1: 4.00; Step 2: 2.00; Step 3: 2.00); SyN (Step 1: 1.00; Step 2: 0.75; Step 3: 0.50); Gaussian regularization (Step 1: 3.00; Step 2: 2.00; Step 3: 1.00); steps (Step 1: 50×1×1; Step 2: 1×50×1; Step 3: 1×1×40)]. A summary of these image processing procedures is provided in Supplemental Materials.

The log Jacobian images were calculated from the Step 1-3 deformation fields and spatially normalized to the symmetrical template. Examples of the Jacobian determinant images are shown for individual participants in Figure 1 and Supplemental Figure 1, which demonstrate the different spatial scales of resolution for each warp and individual differences in warping (Steps 1-3). To quantify the differences in spatial resolution between each normalization step, fast Fourier transforms were applied across XY-, XZ-, and YZ-orthogonal vectors in the normalized Jacobian determinant images from each normalization step with a fixed length of 128 mm. This approach provided a measure for the width of light/dark cycles in the structural warping values that are distributed around zero in the Jacobian Determinant images. Step 1 normalization parameters characterized large-scale deformations (average = 0.008 ± 0.001 cycles per mm) in comparison to Step 3 normalization parameters that characterized small-scale deformations (average = 0.061 ± 0.011 cycles per mm), while Step 2 exhibited some spatial overlap with Steps 1 and 3 (average = 0.011 ± 0.006 cycles per mm). Supplemental Figure 1 presents the spectral power differences across spatial frequencies for each normalization step to demonstrate the peak and range of spatial frequencies or size of structures normalized. Finally, the normalized Jacobian determinant images from each normalization step and the combined steps (All Warps) were smoothed with a Gaussian kernel (FWHM = 8 mm) as in previous structural asymmetry studies and left-right subtracted to create hemispheric asymmetry images.

Directional gray matter asymmetries were also examined for spatial comparison to the directional deformation-based asymmetries to determine the extent to which gray matter and deformation-based asymmetries provided complementary information or qualitatively different spatial patterns of asymmetry. The SPM12 segmented images were normalized to the symmetrical template space using the normalization parameters from the procedure described above. We chose not to modulate or scale the gray matter values by the deformation parameters to identify significant gray matter asymmetries that were independent of the modulation effects. These gray matter density images were smoothed with an 8 mm Gaussian kernel before creating the left-right asymmetry images. Because the gray matter images were not log-scaled like the Jacobian images, scaled gray matter asymmetries were computed as $(L - R) \div \overline{LR}$, where L is the gray matter probability in the left hemisphere voxel, R is that value from the corresponding right hemisphere voxel, and $\overline{LR}$ indicates the average of L and R .

2.3 Replication and Code Sharing.

The image processing scripts used in this study are available at the following URL to facilitate replication and disseminate the methods: https://www.nitrc.org/projects/structural_asym.

2.4 Statistics.

Standard directional asymmetry analyses were performed for each normalization step (1-3), as well as for the Jacobian images that reflect volumetric displacement across all three normalization steps. The regression model for each set of images included dummy variables to control for potential research site effects, age, sex, and TICV. The statistical control for latent research site effects included adjusting for effects of varied image acquisition

parameters (Eckert et al., 2016), such as field strength (1.5 T to 3.0 T) and resolution ($0.9 \times 0.9 \times 0.8$ mm to $1.3 \times 1.3 \times 1.3$ mm). Threshold free cluster enhancement (TFCE) family-wise error correction was used to control for multiple comparisons (TFCE SPM Toolbox, C. Gaser) and identify significant asymmetries in volumetric displacement relative to the symmetrical template. To further investigate the deformation-based asymmetries, 8 mm radius spheres positioned at the peak of the effects were used to collect asymmetry values across subjects.

Finally, analyses were performed to identify potential fluctuating asymmetries. Platykurtic distributions that could reflect fluctuating asymmetries were characterized with the Bonnett test for kurtosis (Bonnett & Seier, 2002) using the Moments R-package (version 0.14; <https://cran.r-project.org/web/packages/moments/index.html>). Bimodal distributions or anti-asymmetries, which could reflect highly leftward and rightward asymmetries that are evenly distributed across populations, were characterized with the Hartigan's Dip Test Statistic for Unimodality (Hartigan, 1985) using the diptest R-package (version 0.75-7; <https://cran.r-project.org/web/packages/diptest/index.html>). These analyses were performed by importing the images into the R statistics environment (R Core Team, 2016) using the AnalyzeFMRI R-package (version 1.1-17; <https://cran.r-project.org/web/packages/AnalyzeFMRI/index.html>). The Bonnett test, in particular, is a relatively conservative approach for identifying fluctuating asymmetries compared to the approach of taking the absolute value of the difference between homologous morphologic measurements (Euler et al., 2008). Each set of deformation-based asymmetries was examined for fluctuating asymmetries based on this absolute value approach and these analyses were limited to voxels where there was no directional asymmetry effect ($p < 0.05$, uncorrected). The results are not shown because they included all regions that did not exhibit directional asymmetries.

3. Results

3.1 Directional Asymmetries.

Figure 2 shows deformation-based asymmetries that have been observed in gray matter asymmetry studies when Jacobian modulation was used, including leftward planum temporale asymmetry, leftward anterior insula asymmetry, rightward superior temporal sulcus asymmetry, rightward frontal and leftward occipital petalias, and rightward temporal pole asymmetry (Eckert et al., 2008; Good et al., 2001; Watkins et al., 2001; and cortical volume: Maingault et al., 2016). The results from the current study indicate that some of the findings from voxel-based gray matter (modulated) asymmetry studies can be attributed to hemispheric differences in gross volumetric displacement that are represented in normalization-based deformation fields rather than specific structural differences in gray matter volume. This is most clearly seen for the medial planum temporale / Heschl's gyrus (Figure 2: top row) and frontal petalia (Figure 2: bottom row), where the deformation asymmetry effects were observed in the underlying white matter. The frontal petalia effect occurs where there is a significant unmodulated gray matter asymmetry (Figure 3). Here, modulation of the gray matter values by the deformation parameters, which are influenced by the underlying white matter volume, would exaggerate a gray matter asymmetry effect. Figure 3 also shows that there can be spatially unique gray matter asymmetry effects

compared to the Jacobian asymmetries, particularly at the lateral cortical boundary, at least for the family-wise error corrected threshold used in this study.

Inspection of the deformation-based asymmetry results from each normalization step revealed that structures like the medial planum temporale, anterior insula, and superior temporal right sulcus had asymmetries requiring all three normalization steps to align these brain regions with the symmetrical template. Participants with relatively greater asymmetry at Step 1 also had greater asymmetry at subsequent steps (e.g., medial planum temporale asymmetry, peak effect from the combined warp asymmetry: Step 1 * Step 3: $r_{(346)} = 0.38$, $p = 2.51E-13$).

There were asymmetries that were most pronounced at specific normalization steps. For example, Figure 2 shows that rightward frontal petalia was most pronounced for the large-scale Step 1 warping and again indicates that frontal white matter volume contributes to this asymmetry. Some of the structural asymmetries were most pronounced at Step 3. For example, the forceps minor exhibited a significant leftward asymmetry (Figure 2, second row oval). This Step 3-specific effect is clearly represented in histograms of forceps minor asymmetry for each normalization step and appeared to be due to the smaller anterior-to-posterior thickness of the right compared to left forceps minor (Figure 4). Leftward forceps minor asymmetry was most pronounced in participants with greater Step 1 rightward prefrontal asymmetry ($r_{(346)} = 0.23$, $p = 2.70E-5$), suggesting that surrounding brain structure influenced the width of the right forceps minor.

As a form of validation for the deformation-based morphometry approach and to further demonstrate the value of examining deformation fields from each normalization step, TICV and demographic variables that were included as covariates in the one-sample t-test results described above were also examined for associations with the deformation-based asymmetries. Figure 5 shows that TICV was significantly related to Step 1 leftward asymmetry in the internal capsule (posterior limb), hippocampus, and superior parietal lobule, but there were no significant TICV effects for Steps 2 and 3. Figure 5 also shows that age was significantly associated with the Step 3 asymmetries in a posterior external capsule / putamen and cerebellar hemisphere regions, but there were no age significant effects for Steps 1 and 2. The external capsule / putamen asymmetry was rightward in younger children and exhibited decreasing rightward asymmetry with increasing age. In contrast, cerebellar asymmetry was increasingly rightward with increasing age. Finally, there were no significant main effects of sex.

3.2 Anti- and Fluctuating Asymmetries.

There was no evidence of significant anti-asymmetries for normalization Steps 1-3, at least based on Hartigan's Dip Test statistic (all Hartigan values < 0.032 , $ps > 0.10$). There were asymmetries at each normalization step that exhibited significant differences from normality based on the Bonnett test. However, these effects were all leptokurtic and largely in midline regions that exhibit relatively low anatomical variance (Figure 6 red regions). Inspection of the kurtosis values across the brain revealed that few voxels trended towards a platykurtic distribution. The lowest kurtosis across normalization steps was observed in the Step 1 superior temporal sulcus where there is typically high sulcal / gyral variability (kurtosis =

2.27; $z = -2.77$), but this effect was not significant after multiple comparison correction. Thus, there was not strong evidence of fluctuating asymmetries in the warping parameters across the three spatial scales of normalization based on evidence of a platykurtic distribution.

4. Discussion

The results of this study demonstrate that structural asymmetries at different spatial scales of resolution can be identified using a multi-step normalization procedure with increasingly finer warping parameters. The deformation-based asymmetry approach used in the current study identified many of the directional structural asymmetries that are reported in gray matter asymmetry studies (Good et al., 2001; Watkins et al., 2001), which were represented at all three normalization steps (e.g., medial planum temporale). The approach also characterized asymmetries that have not been reported, and which occurred for specific normalization steps where there was variation in asymmetries that were significantly associated with TICV and age. The deformation-based asymmetry approach was not sensitive to fluctuating asymmetries, as defined by significant a platykurtic distribution, but can demonstrate fluctuating asymmetries based on a measure of the absolute value of the hemispheric differences in Jacobian determinants.

The results from this study have relevance not just for studies of cerebral asymmetries, but also for other voxel-based structural studies where warping parameters are combined across normalization steps to examine structural asymmetries (Figure 2). Specifically, larger-scale asymmetries were observed to obscure some smaller-scale asymmetries. Thus, a standard voxel-based asymmetry analysis involving gray matter modulation by the deformation fields will emphasize results due to larger scale gross morphologic features and perhaps the underlying white matter compared to locally specific gyral/sulcal effects (Barrick et al., 2005). The results of the current study demonstrate the value in optimizing normalization parameters to leverage specific stages of normalization that can enhance sensitivity to large and small brain structures of interest.

Like any voxel-wise approaches, the deformation-based asymmetry approach described here has limitations and relative strengths. The standard gray matter volume asymmetry approach involving modulation lumps together gray matter density, volumetric, and shape effects. Here we have shown the impact of uncoupling gray matter density and volumetric or deformation information, which appeared to be strongly influenced by white matter morphology. However, deformations can still be influenced by qualitative differences in sulcal/gyral features. The development of templates with qualitatively distinct features that are a focus of study can limit this confound and would enhance the rigor of voxel-based studies when sample sizes are sufficiently large to define groups of subjects with common shape features.

4.1 Directional Asymmetries.

The normalization parameters and number of normalization steps used for the current study were chosen as a proof of concept to demonstrate that unique patterns of asymmetries are present at different scales of resolution. Examination of the Jacobian determinant images

(Figure 1) and group results (Figure 2) indicated that the three normalization scales of resolution were sensitive to lobar (Step 1), regional or fissure (Step 2), and gyral/sulcal features (Step 3), respectively, which generally corresponds to the measured spatial frequencies of the Jacobian determinant images from each normalization step (Supplemental Figure 1). These observations are consistent with evidence that morphologic effects can be present at the voxel level or in larger volumetric and surface area measures (Eckert et al., 2005; Voormolen et al., 2010).

An unexpected asymmetry result was the observation that the forceps minor was narrower in the right hemisphere than left hemisphere. One methodologic explanation for this result is that normalization at the first normalization step moved prefrontal areas too much and affected the space of the forceps minor that was corrected in the subsequent smaller scale warping steps. An association between the Step 1 prefrontal asymmetry and the Step 3 forceps minor asymmetry appears to support this explanation, but this association was small and accounted for only 6% of the variation in the forceps minor deformation. Moreover, asymmetry of the forceps minor was reported in a diffusion imaging study, which demonstrated that variance in forceps minor asymmetry was predicted by shared environmental factors (Jahanshad et al., 2010). In contrast, morphologic variation in other major fiber tracts were more strongly predicted by genetic effects in the sample of monozygotic and dizygotic twins. There was not clear evidence for environmental variables that contributed to the effects of the current study. It is possible that an expansion of the right lateral ventricle (anterior horn) due to perinatal events could contribute to this asymmetry, although ventricle enlargement was not seen for the participant shown in Figure 4 and would not be expected with sufficient frequency in this normative sample to produce a significant group-level effect.

The most pronounced asymmetries in regions like the right prefrontal cortex, medial planum temporale / Heschl's gyrus, and superior temporal sulcus were not influenced by TICV or demographic variables. There were regions of the internal capsule (PL), hippocampus, and superior parietal lobule where greater TICV was significantly associated with more leftward asymmetry. These TICV effects were observed only for the Step 1 normalization where the largest scale normalization parameters were sensitive to lobar size effects and occurred in similar locations where TICV was related to cortical thickness in a large multi-site study (Kong et al., 2018). In addition, there was an absence of sex differences in deformation-based asymmetries. This result was surprising given that sex has been related to voxel-based and cortical thickness asymmetries in previous studies (Good et al., 2001; Kong et al., 2018; Luders et al., 2004), but not in every study (Watkins et al., 2001). One explanation for this discrepancy with some of the extant literature is that TICV and sex were both included as covariates in the analyses. Leonard et al., (2008) showed that sex differences in perisylvian and corpus callosum measures were largely explained by total brain volume. Indeed, few sex differences in gray matter asymmetry have been observed when males and females are matched for total brain volume (Kurth et al., 2018).

4.2 Anti- and Fluctuating Asymmetries.

The deformation-based asymmetry methods were not sensitive to fluctuating asymmetries, at least with respect to asymmetries that exhibit a platykurtic distribution (Vallortigara & Rogers, 2005). We expected that fluctuating asymmetries might be demonstrated in sulcal/gyral morphology differences between hemispheres. For example, the diagonalis sulcus of the inferior frontal gyrus is variably present across cerebral hemispheres (Ono, Kubik, & Abnerthy, 1990), but asymmetry in this region did not exhibit a significant platykurtic distribution. This region did exhibit evidence of fluctuating asymmetry when the absolute value of the asymmetry images was examined, as in studies of fluctuating skeletal asymmetries (Euler et al., 2008). Again, all brain regions that did not exhibit a directional asymmetry ($p < 0.05$, uncorrected) were regions that exhibited fluctuating asymmetry with the absolute difference method and may reflect random developmental organization reflecting, at least in part, environmental events (Van Valen, 1962). Perhaps the shift of the posterior external capsule/putamen towards symmetry with increasing age reflects this type of fluctuating asymmetry, but it is unclear what events might influence this asymmetry from ~7-13 years of age. Finally, it is possible that the deformation-based approach described here is sensitive to fluctuating asymmetries in low cognitive function samples (Banks et al., 2010) and clinical populations compared to this normative sample.

4.3 Multi-site Study Limitations.

Significant structural asymmetries were observed across the multi-site sample when including images that were collected at different research sites with different scanner hardware and T1-weighted sequences. Site differences were controlled by using dummy variables representing each site in the regression analyses. This statistical approach of controlling for site effects reduces the likelihood that any one site could contribute to the group-level asymmetry effects observed in this study (Figures 2, 3, 4, 6). Sensitivity to individual differences in sex and age could have been diminished because controlling for site effects would also control for site differences beyond scanner hardware and sequence variables, such as demographic variables. There were no significant differences in the frequency of sex across the sites ($\chi^2_{(7)} = 9.21$, $p = 0.24$), but there were site differences in age. While multiple sites had age distributions that reflected the distribution of the entire sample, there were sites with a preponderance of children above or below the median age of the multi-site sample ($\chi^2_{(7)} = 83.69$, $p < 0.001$). For example, 33 or 34 children from site 3 were above the median age of the multi-site sample, while 26 of 33 children from site 4 were below the median age. Thus, the age-related results described here may be an underestimate of age and structural associations.

4.4 Conclusions.

Together, the results suggest that there are unique mechanisms for the development of asymmetries at locally specific and gross morphologic scales of measurement. Some of these asymmetries could be due to genetic and epigenetic patterning (Schmitz et al., 2017) that produce mechanical forces (Ferreira & Vermot, 2017) on the developing brain, while others may be related to experience (Sun et al., 2012), which may explain when and if structural asymmetries map to functional asymmetries. The methods demonstrated here

show that: 1) gray matter and deformation-based approaches can provide complementary information about asymmetries that may have unique etiologies; 2) there are few platykurtic distributions in deformation data that can be considered evidence of fluctuating asymmetries; and 3) normalization parameters can be tailored for a specific spatial scale of resolution, particularly for small structures where variance may be underestimated because of the influence of gross volumetric deformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Cerebral structural asymmetries were identified using deformation-based morphometry.
- The method is complementary to gray matter asymmetry methods.
- The method can be tailored to structures at specific scales of resolution.
- Brain volume and age uniquely predicted asymmetries at different scales of resolution.
- The method was most sensitive to directional rather than fluctuating asymmetries.

Figure 1.

The log Jacobian images from the combined warps (All Warps) and each normalization step are presented for two participants (rows) with rightward (A) and leftward planum temporale asymmetry (B). This different pattern of asymmetry can be seen in the relatively larger Jacobian values in the red ovals. Note too the increased spatial specificity of the Jacobian values or degree of warping with each normalization step.

Figure 2.

Group-level deformation-based asymmetries displayed in neurological convention. **All Warps.** Consistent with voxel-based findings, there were significant leftward asymmetries in the medial planum temporale/Heschl's gyrus, occipital pole, and anterior insula/inferior frontal gyrus asymmetries, as well as significant rightward asymmetries in the superior temporal sulcus, medial temporal lobe, and frontal pole (TFCE, FWE $p < 0.05$). **Step 1 Warps.** The large scale or spatially broad asymmetry effects in the All Warps results were largely due to the first normalization step where relatively gross normalization parameters were used to align large features of the images to the template image, as seen in Figure 1. **Step 2 Warps.** Results from this normalization step reflect the intermediate spatial scale of warping between the Step 1 and 3 normalization parameters and for this reason characterize relatively large features that were not completely normalized in Step 1 and smaller scale features that are represented by Step 3. Note that Steps 2 and 3 were more sensitive to smaller scale asymmetries, including in the frontal operculum, for example. **Step 3 Warps.** Smaller scale asymmetries on the spatial scale of sulcal/gyral features appear to be best characterized by the final normalization step, as shown within the red ovals where the asymmetry effects are most pronounced at Step 3. Some asymmetries were so pronounced

that all three normalization steps were required to align structures like the medial planum temporale/Heschl's gyrus and superior temporal sulcus.

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Figure 3.

Significant unmodulated gray matter asymmetries (green) and deformation-based or Jacobian asymmetries (red: All Warps) are shown in regions that were asymmetric in both datasets (yellow). The orange arrow (top left) demonstrates that gray matter in parietal cortex exhibits a significant leftward asymmetry, which was not observed in the Jacobian images. The blue arrow (bottom right) demonstrates a frontal cortex region where gray matter asymmetry would be exaggerated by the underlying asymmetry in white matter when gray matter data are modulated by the corresponding Jacobian determinant data.

Figure 4.

Demonstration of a significant asymmetry at the smallest spatial scale of resolution (highlighted in Figure 2). **A.** Significant group-level forceps minor asymmetry was most pronounced at Step 3 (orange arrow; TFCE, FWE $p < 0.05$). **B.** A smoothed and normalized Jacobian determinant image from a representative subject is displayed to show the forceps minor region that was enlarged in the right hemisphere to match the symmetrical template (darker blue region over right forceps major). **C.** The T1-weighted image used to generate the Jacobian determinant image in B exhibits a narrow right hemisphere forceps major (orange arrow) relative to the left hemisphere forceps minor. **D, E, F.** Histograms. An 8 mm radius sphere was centered at the peak of the forceps minor result in A and was used to collect the average asymmetry in this region across subjects for the Step 1 (**D**), Step 2 (**E**), and Step 3 (**F**) asymmetry images to demonstrate the shift in asymmetry values at each normalization step. This highlights the relative symmetry at Steps 1 and 2, compared to smaller-scale asymmetries obtained at Step 3, across participants.

Figure 5.

Total intracranial volume and age effects on the deformation-based asymmetries. **A.** The significant associations between total intracranial volume and the Step 1 asymmetries were focused in the posterior limb (PL) of the internal capsule and overlapped with the regions exhibiting significant effects across the sample (yellow; TFCE, FWE $p < 0.05$). These effects extended down to the hippocampus and cerebral peduncle (green) and included a separate cluster in the superior parietal lobule (green). **B, C.** Age was significantly associated with Step 3 asymmetries in the posterior external capsule and putamen, as well as in the lateral cerebellar hemisphere (cyan). **D, E.** Scatterplots of the effects shown in **A** and **B**. Leftward asymmetry of the internal capsule (PL) region increased with total intracranial volume, while an external capsule asymmetry became symmetric with increasing age (median age split at 9.71 years: younger children: $t_{(172)} = -5.28$, $p = 2.70\text{E-}8$; older children: $t_{(173)} = -1.10$, $p = 0.27$).

Figure 6.

Group-level kurtosis is shown for Jacobian images from Steps 1-3. While leptokurtic distributions were present in midline regions across subjects, there was limited evidence of platykurtic distributions. Mirror-image effects are observable across hemispheres because there are inverse asymmetry values between hemispheres that exhibit to same distribution despite having the opposite sign. Green regions (kurtosis = 3) represent voxels with a mesokurtic distribution. Red regions represent voxels with a leptokurtic distribution (across voxels and Steps 1-3, highest kurtosis value = 9.87; $z = 6.30$; cerebellar white matter / fourth ventricle boundary in Step 2). Blue regions represent voxels trending towards a platykurtic

distribution or fluctuating asymmetry, but there were no significant platykurtic distributions after multiple comparison correction (across voxels and Steps, lowest kurtosis value = 2.27; $z = -2.77$; superior temporal sulcus in Step 1). The bottom row shows the corresponding sections from the symmetrical template for comparison with the kurtosis data in each column.