The Feasibility of a Common Stereotactic Space for Children and Adults in fMRI Studies of Development

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Received October 25, 2001

INTRODUCTION

Recently, with the increased availability of noninvasive neural imaging techniques such as magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), neuroscientists have begun to examine brain development in healthy children. MRI and fMRI offer powerful methods for tracking structural and functional development in the maturing brain and have added considerably to the study of human neural development (e.g., O'Tuama et al., 1999; Eliez and Reiss, 2000; Rivkin, 2000). However, use of these tools in children presents certain methodological problems that remain unsolved (e.g., Bookheimer, 2000; Gaillard et al., 2001).

One critical issue pertains to the ability to compare directly image data between children and adults. Comparisons across adults, and adult populations, are often made through the stereotactic or spatial normalization of individual brains to a common anatomic frame of reference (Fox et al., 1988; Friston et al., 1991). Spatial normalization of brains to a common template permits researchers to make direct statistical comparisons between groups of subjects within the same stereotactic space. In studies involving adult populations only, individual brains are normalized to a template derived from an adult brain (or several adult brains). However, the accuracy with which pediatric brains may also be transformed into such a space is questionable. Indeed, many developmental neuroscientists have been reluctant to transform pediatric brains into an adult-derived space for fear that child brains are too morphologically different to be compared effectively with adult brains. For example, Gaillard and colleagues (2001) have suggested that “smaller brain size and age-dependent differences in proportional brain region size will affect warping children’s brain images into standard atlases commonly employed for [adult] group analysis” and “the distortion engendered by warping children’s brains into an adult atlas will influence group analysis and comparisons across ages are likely to be in error . . . .” (p. 242).

These concerns regarding the use of the anatomical normalization techniques for the comparison of child and adult neuroimaging data have merit. Normal brain development in children involves many matura-
tional changes that could affect the extent to which child and adult neuroimaging data may be normalized within the same stereotactic space. In particular, between the ages of about 2 and 14 years, total brain matter increases in volume by about 25% (Caviness et al., 1996; Reiss et al., 1996; Giedd et al., 1996). The ratio of apparent gray to white matter volumes changes, with gray matter increasing until about age 8 and then decreasing and white matter increasing until about age 30 before decreasing (Pfefferbaum et al., 1994; Giedd et al., 1999; Sowell et al., 1999; Courchesne et al., 2000). Finally, child brains have been demonstrated to be more variable than adult brains in terms of overall shape, as assessed through statistical parametric mapping (Muzik et al., 2000) and the size of certain brain structures (Lange et al., 1997). These anatomical and variability differences between child and adult brains may have critical consequences for the use of brain normalization for functional comparisons.

However, the reluctance to rely on similar transformations for child and adult data has limited functional imaging research by limiting direct statistical comparisons of subject groups. For example, in an investigation of children and adults performing an “n-back” task for spatial memory, Thomas and colleagues (1999) transformed pediatric brains to an “average” brain from their group of child subjects and transformed adult brains to an “average” brain from the group of adult subjects. Because child and adult data were normalized within two different spaces, the two groups could not be subjected to direct group-wise analyses.

The self-imposed limits on research using standard spaces for child and adult images reinforce the need for direct investigations of differences in child and adult neuroanatomy when transformed into a single standard space. For this reason, the present studies address empirically and through simulation the impact of anatomical differences between child and adult brains in the context of fMRI studies. In order to interpret the relative magnitude of anatomical and functional variability in this context, an estimate of the resolution of the functional imaging data is necessary. Typically, fMRI images are collected at a resolution of approximately 3 x 3 mm in plane with slice thickness ranging from 3 to 8 mm. Often, the raw data are smoothed by varying amounts. Also, resampling during transformation of the image (e.g., warping to a different space) additionally smooths the images. With these considerations, a conservative estimate of the effective resolution of typical functional imaging data is greater than 5 mm (and more likely greater than 7 mm). The effect of differences in location and variability between adult and child imaging data must be considered in the context of this level of resolution.

Previous research on spatial normalization procedures for child and adult images suggests that transformation of pediatric brains to stereotactic space, while not effective for children below the age of 6 years, may be possible for older children (Kaplan et al., 1997; Muzik et al., 2000). Moreover, children less than 6 years of age often are difficult to study by current fMRI methods due to task-performance and motion-related issues (Gaillard et al., 2001). Thus, in Study 1, differences between 7- and 8-year-old child and adult brains were investigated after transforming child and adult anatomical images into a common, adult-derived space based on the Talairach Atlas (Talairach and Tournoux, 1988). In Study 2, the effect of anatomical differences on functional comparisons was assessed through simulation of fMRI responses in subjects displaying group location and variability differences of the magnitude measured in Study 1.

**STUDY 1**

Potential differences in pediatric and adult brains were examined by comparing (a) the coordinates corresponding to portions of selected sulci and (b) the coordinates corresponding to the outer boundary of the brain (in three planes), in a group of 7- and 8-year-old children and a group of young adults. Sulci measurements provide information about internal variations in brain shape and have been used previously to assess anatomy across development (Sowell et al., 2002). In contrast, outer-boundary measurements provide an estimate of overall external brain shape. We assessed these measurements in two ways: (1) by examining differences between coordinate locations in children and adults and (2) by examining differences in the variability of these locations between children and adults. If 7- and 8-year-old children’s brains differ substantially from adult brains after normalization to an adult-derived stereotactic space, then significant differences in coordinate locations should be observed between children and adults both in overall shape and in internal landmarks. Likewise, if 7- and 8-year-old children’s brains are significantly more variable than adult brains, then there should be consistently greater variance in the child than in the adult measurements.

**Method**

Subjects

Structural images were obtained from 20 adult (10 female; mean age 22.5 ± 2.8; range 18–30 years) and 20 child (10 female; mean age 8.1 ± 0.8; range 7–8 years) volunteers from the Washington University community. Child subjects were determined to be neu-

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2 It may be important to note that Muzik and colleagues (2000) examined children with epilepsy, whereas Lange and colleagues (1997) tested normal subjects exclusively.
rologically normal through examination by a pediatric neurologist (B.L.S.) and/or by completing a detailed history-of-physical-condition questionnaire. Adult subjects were screened using another detailed questionnaire to ensure that they had no history of neurological or psychiatric problems. Adult subjects and parents of child subjects gave informed consent, and child subjects gave assent, in accordance with the guidelines and approval of the Washington University Human Studies Committee. All subjects were paid for their participation.

Image Acquisition

Sagittal 3D, T1-weighted images were acquired on a Siemens 1.5-T Vision scanner (Erlangen, Germany) using the standard circularly polarized head coil. MP-RAGE sequence (Muglar and Broekman, 1990) particulars were voxel size $1 \times 1 \times 1.25$ mm voxels. TR = 9.7 ms, TE = 4 ms, flip angle $12^\circ$, TI = 300 ms, and TD = 0 ms. At the beginning of each session, the main field was shimmed to a tolerance of $<0.1$ ppm. A pillow and a thermoplastic face mask were used to minimize head movement. Headphones dampened scanner noise and enabled communication with subjects.

Spatial Normalization

Stereotactic registration was accomplished by 12-parameter affine warping of individual MP-RAGE images to an atlas-representative target using difference image variance minimization as the objective function (Snyder, 1996). The method differs from that incorporated into SPM only in the image used as the atlas-representative target (Evans et al., 1995). The common strategy was first described in application to positron emission tomography-based functional neuroimaging by Collins and colleagues (1994). Our atlas-representative target was prepared by 12-parameter affine coregistration of MP-RAGE images representing an independent group of 12 neurologically normal young adults (ages 18–35 years). One subject, selected on the basis of visual inspection as being most typical, was used as the target for the remaining 11. The 12-subject average was made to conform to the Talairach Atlas (1988) using the SN method of Lancaster et al. (1995). The SN-derived transform and the individual coregistrations were algebraically composed to yield 12 affine transforms. These transforms then were used to create the atlas-representative image by resampling (to 2-mm cubic voxels) and averaging using one interpolation per subject.

In the present work all measurements were made on atlas-transformed data resampled to 1-mm cubic voxels. Figure 1 depicts the average of the 20 adult images and the average of the 20 child images, after spatial normalization of each image. The sections displayed are those that were chosen for the outer-boundary measurements. Qualitatively, the child- and adult-averaged images are similar, suggesting the feasibility of atlas transformation for child and adult brains. To assess anatomical differences between the two groups quantitatively, sulci and outer-boundary measurements were obtained.

Sulcus and Outer-Boundary Measurements

After image normalization, we chose 10 sulci, widely distributed across the cerebral cortex, that were consistently identifiable in the same section in a small number of adult subjects from the present sample and in an additional group of 9- and 10-year-olds. In the sagittal plane, the superior temporal sulcus (in Talairach plane $x = 51$; Talairach and Tournoux, 1988), the inferior frontal sulcus ($x = 45$), the cingulate sulcus ($x = 7$), and the parieto-occipital sulcus ($x = 5$; see right side of Figs. 2 and 3) were identified. In the coronal plane, the superior frontal sulcus ($y = 25$), the ascending ramus of the Sylvian fissure ($y = 25$), and the calcarine sulcus ($y = -57$; see right side of Fig. 4) were identified. In the horizontal plane, the central sulcus ($z = 60$), the lateral border of the posterior insula ($z = -2$), and the occipital sulcus ($z = -20$; see right side of Fig. 5) were identified. For the outer-boundary measurements, we chose two sagittal sections ($x = 15/–15$), a coronal section ($y = 25$), and a horizontal section ($z = 10$; see Figs. 6 and 7).

After having identified the sections that would be used for the sulcus and outer-boundary measurements, we chose coordinates along each to be plotted in every subject. Because these coordinates were predetermined and held constant across all subjects, they were “fixed” and are referred to as such hereinafter. For the sulci measurements, between three and six fixed coordinates in 5-mm increments that extended along each sulcus in a single direction were chosen. For example, Fig. 2 depicts the five fixed coordinates that we chose to plot for the superior temporal sulcus. Z values along this sulcus were plotted for the coordinates $y = -10$, $y = -15$, $y = -20$, $y = -25$, and $y = -30$ in section $x = 51$. Effectively, a line was placed at each fixed y coordinate, and the z coordinate where the sulcus intersects that line was extracted. The fixed coordinates for each sulcus are depicted in Figs. 2–5 on the x axis of the graph corresponding to each.

Outer-boundary measurements were extracted in a manner similar to sulci measurements. For the sagittal-section measurements, z values at 12 fixed y coordinates in 15-mm increments along the anterior surface of the cortex were plotted in each hemisphere (see top right of Fig. 6). For the coronal-section measurements, x values at 9 fixed z coordinates in 10-mm increments were plotted in each hemisphere (see top right of Fig. 7). For the horizontal-section measurements, x values at 12 fixed y coordinates in 15-mm
increments were plotted in each hemisphere (see bottom right of Fig. 7).

Each sulcus and each outer boundary was plotted in each subject by two researchers (the first author and a trained research assistant) using in-house software that allows designated slices from structural images to be viewed in two dimensions and Talairach coordinates (Talairach and Tournoux, 1988) within that slice to be plotted. When plotting the sulci, if a sulcus location at a fixed point was not immediately apparent, sulcus plotters chose coordinates in the darkest (and thus presumably deepest) area of the sulcus or, when no obvious dark area was apparent, chose coordinates in the middle of the sulcus. If a sulcus was not present at one of its fixed coordinates, then no value was entered for that location, and empty cells were later replaced with the mean for that condition to avoid statistical complications associated with missing values. The missing values did not seem to systematically come from either group or any individual subject. The sulcus most affected was the lateral border of the posterior insula with 4.4% missing values. Of these missing values, 43% came from the child group and 57% came from the adult group. For all other sulci, missing values comprised less than 2% of the total number of observations.

When plotting the outer boundaries of each section, plotters most often simply chose coordinates along the brain/nonbrain border in the image. However, in order to avoid underestimating the outer-boundary measurements, plotters interpolated across invaginations in the outer boundary created by sulci. For example, in the coronal section shown in Fig. 7A, the measured points for fixed coordinate $z = 65$ in both hemispheres are plotted on the interpolated surface, rather than on the brain/nonbrain boundary. It is important to note, however, that instances in which interpolation was necessary were rare, as may be observed in Figs. 6 and

**FIG. 1.** The average of the 20 adult images and the average of the 20 child images, after each image was spatially normalized to a common stereotactic space. The sections displayed are those that were chosen for the outer-boundary measurements.
Moreover, since plotters were able to obtain values at each of the fixed coordinates, missing values were not an issue for the outer-boundary analyses.

### Statistical Analyses

The first step in our analyses was to assess the extent to which the two plotters’ values were in agreement. To this end, we measured interrater reliabilities between the plotters’ values at each of the fixed coordinates for each sulcus \((n = 45)\) and each outer-boundary section \((n = 66)\), using a Pearson’s \(r\) correlation coefficient. Overall, correlation coefficients were high (mean \(0.91 \pm 0.05\); all \(P < 0.0001\)). However, correlations for the sulci tracings were slightly higher (0.90–0.99) than correlations for the outer boundary tracings (0.81–0.95). No other systematic variations in the correlations were apparent. Because of their overwhelming similarity, the plotters’ values were averaged and the mean of their values on each fixed coordinate in each sulcus and outer-boundary section for each subject was used as the dependent measure in all subsequent analyses. The averaged values for each fixed coordinate of each sulcus and each outer-boundary section for a single adult subject are displayed on the right sides of Figs. 2–7.

To examine differences in location of child and adult sulci and outer boundaries, a separate, repeated-measures analysis of variance (ANOVA) was conducted for each of the 10 sulci and each of the three outer-boundary sections. As noted above, the dependent measure was the mean plotted value (across the two plotters) in each analysis. Age of subject (adult vs child) was a between-subjects independent variable in all analyses. In addition, fixed coordinate was a within-subjects independent variable in all analyses, although the number of levels for this variable differed depending on how many coordinates were plotted for a particular sulcus or outer boundary (e.g., five fixed coordinates were plotted for the superior temporal sulcus; for this analysis, the fixed-coordinate variable had five levels). Finally, hemisphere (left vs right) was included as a within-subjects independent variable in the three outer-boundary analyses.\(^3\)

To examine differences in location variability in children and adults, we conducted \(F\) tests for the equality of variances across child and adult groups. \(F\) tests

\(\text{FIG. 2. Results from the analysis of the superior temporal sulcus, } x = 51.\) On the left side plotted \(z\) values are displayed as a function of fixed \(y\) value and age. Error bars indicate standard errors of the mean. A representative sulcus from a single adult subject is depicted on the right. Red dots indicate the mean value (across the two plotters) of each plotted coordinate for this subject.

\(\text{FIG. 3. Results from analyses of the inferior frontal sulcus (} x = 45\text{)} (A), the cingulate sulcus (} x = 7\text{) (B), and the parieto-occipital sulcus (} x = 5\text{) (C). On the left (A–C), plotted values are displayed as a function of fixed coordinate and age. Fixed values are depicted on the } x\text{ axis and plotted coordinates are depicted on the } y\text{ axis for each sulcus. Error bars indicate standard errors of the mean. A representative sulcus from a single adult subject is depicted on the right (A–C). Red dots indicate the mean value (across the two plotters) of each plotted coordinate for this subject.}\)
comparing variance in children and adults across all fixed coordinates and for each fixed coordinate individually were performed for each sulcus and each outer-boundary section. As in the previous analyses, mean plotted value (across the two plotters) was the dependent measure in each analysis.

**Results**

In order to ensure that we did not overlook possible differences between adult and child groups, all effects reaching a significance level of $P < 0.05$ uncorrected are reported in the text below. However, in light of the large number of comparisons made, both uncorrected and Bonferroni-corrected $P$ values are reported when relevant. Significance values corrected for 10 multiple comparisons in the case of sulci (denoted $P_{10}$), 3 multiple comparisons in the case of outer boundaries (denoted $P_{3}$), and 13 multiple comparisons for all ANOVAs performed in Study 1 (denoted $P_{13}$) are reported in addition to uncorrected values.

**Locations of Sulci**

The left sides of Figs. 2–5 depict the results from the 10 repeated-measures ANOVAs assessing differences in sulcus locations between groups. Three of the 10 sulci examined (the superior temporal sulcus, the parieto-occipital sulcus, and the olfactory sulcus) revealed significant effects of age.

![Fig. 4](image-url)

**FIG. 4.** Results from analyses of the superior frontal sulcus ($y = 25$) (A), the ascending ramus of the Sylvian fissure ($y = 25$) (B), and the calcarine sulcus ($y = -57$) (C). On the left (A–C), plotted values are displayed as a function of fixed coordinate and age. Fixed values are depicted on the $x$ axis and plotted coordinates are depicted on the $y$ axis for each sulcus. Error bars indicate standard errors of the mean. A representative sulcus from a single adult subject is depicted on the right (A–C). Red dots indicate the mean value (across the two plotters) of each plotted coordinate for this subject.

![Fig. 5](image-url)

**FIG. 5.** Results from analyses of the central sulcus ($z = 60$) (A), the lateral border of the posterior insula ($z = -2$) (B), and the olfactory sulcus ($z = -20$) (C). On the left (A–C), plotted values are displayed as a function of fixed coordinate and age. Fixed values are depicted on the $x$ axis and plotted coordinates are depicted on the $y$ axis for each sulcus. Error bars indicate standard errors of the mean. A representative sulcus from a single adult subject is depicted on the right (A–C). Red dots indicate the mean value (across the two plotters) of each plotted coordinate for this subject.
Results from the analysis of the superior temporal sulcus are depicted on the left side of Fig. 2. Overall, plotted z values for this sulcus were more dorsal in children \((z = -6.9)\) than in adults \((z = -8.4)\) as reflected by a main effect of age, \(F(1,38) = 12.07, P < 0.005, P_{10} < 0.05, P_{13} < 0.07, \text{MSe} = 9.34\). No other effects in this analysis approached significance.

Results from the analysis of the parieto-occipital sulcus are depicted on the left side of Fig. 3C. This analysis revealed a significant interaction of fixed coordinate \((z = 35, 30, 25, 20, 15)\) by age, \(F(4,152) = 4.43, P < 0.005, P_{10} < 0.05, P_{13} < 0.07, \text{MSe} = 7.99\). Comparison of the means of the relevant groups revealed that on fixed coordinates \(z = 35\) and \(z = 30\), \(y\) values were more anterior in adults \((-76.8\) and \(-73.5\) for \(z = 35\) and \(z = 30\), respectively) than in children \((-81.2\) and \(-77.8\) for \(z = 35\) and \(z = 30\), respectively). No other effects in this analysis approached significance.

Results from the analysis of the olfactory sulcus are depicted on the left side of Fig. 5C. Overall, plotted \(x\) values for this sulcus were more lateral in children \((10.2)\) than in adults \((9.1)\) as reflected by a main effect of age, \(F(1,38) = 8.31, P < 0.01, P_{10} < 0.10, P_{13} < 0.13, \text{MSe} = 6.70\). No other effects in this analysis approached significance.

Locations of Outer Boundaries

The left sides of Figs. 6 and 7 depict the results from the three repeated-measures ANOVAs assessing differences in outer-boundary locations between groups. Significant effects of age and hemisphere were observed in all three of the outer-boundary sections.

Results from the analysis of the sagittal section are depicted on the left side of Fig. 6. This analysis revealed a significant interaction of hemisphere (left vs right) by age (adult vs child), \(F(1,38) = 6.41, P < 0.05, P_{10} < 0.15, P_{13} < 0.65, \text{MSe} = 2.62\). Comparison of the means from these conditions indicates that the difference between \(z\) values for children \((55.3)\) and adults \((54.6)\) was greater in the left hemisphere than in the right hemisphere \((55.6\) and 55.4 for children and adults, respectively). In addition, the interaction of fixed coordinate \((y = 65, 50, \ldots, -85, -100)\) by age was significant, \(F(11,418) = 7.50, P < 0.0001, P_{3} < 0.0005, P_{13} < 0.005, \text{MSe} = 8.06\). Comparison of the means from these conditions indicates that the greatest difference between children \((24.0)\) and adults \((19.3)\) occurred at the endpoint measurement \(y = 65\). Any differences in fit would be magnified here because it is a point of high curvature. Finally, a significant interaction of fixed coordinate by age by hemisphere, \(F(11,418) = 3.25, P < 0.0005, P_{3} < 0.005, P_{13} < 0.05, \text{MSe} = 2.58\), revealed that the difference between children and adults at \(y = 65\) was greater in the left hemisphere \((24.2\) and 17.8 for children and adults, respectively) than in the right hemisphere \((23.9\) and 20.7 for children and adults, respectively). No other effects in this analysis reached significance.

Results from the analysis of the coronal section are depicted on the left side of Fig. 7A. Overall, \(x\) values were more lateral in children \((44.7)\) than in adults \((43.3)\), as reflected by a main effect of age, \(F(1,38) = 15.82, P < 0.0005, P_{3} < 0.005, P_{13} < 0.05, \text{MSe} = 20.82\). A significant interaction of fixed coordinate \((z = 55, 45, \ldots, -15, -25)\) by age (adult vs child), \(F(8,304) = 2.11, P < 0.05, P_{3} < 0.15, P_{13} < 0.65, \text{MSe} = 7.26\), indicated that this difference between children and adults was greatest at \(z = -15\) \((46.2)\) and \((43.1)\) for children and adults, respectively and \(z = -25\) \((14.5)\) and \((12.4)\) for children and adults, respectively). In addition, \(x\) values overall were more lateral in the right hemisphere \((44.4)\) than in the left \((43.6)\), as reflected by a main effect of hemisphere, \(F(1,38) = 37.48, P < 0.0001, P_{3} < 0.0005, P_{13} < 0.005, \text{MSe} = 3.45\). A significant interaction of fixed coordinate by hemisphere (left vs right), \(F(8,304) = 12.70, P < 0.0001, P_{3} < 0.0005, P_{13} < 0.005, \text{MSe} = 2.50\), indicated that this difference between right and left hemispheres was greatest at \(z = 55\) \((29.6)\) and \((27.5)\) for right and left hemispheres, respectively and \(z = 45\) \((42.9)\) and \((40.6)\) for right and left hemispheres, respectively, whereas at \(z = -15\), \(x\) values were more lateral in the left hemisphere \((45.6)\) than in the right \((43.8)\). No other effects in this analysis reached significance.

Results from the analysis of the horizontal section are depicted on the left side of Fig. 7B. Overall, \(x\) values were more lateral in children \((53.5)\) than in adults \((51.7)\), as reflected by a main effect of age, \(F(1,38) = 96.24, P < 0.0001, P_{3} < 0.0005, P_{13} < 0.005, \text{MSe} = 7.95\). A significant interaction of fixed coordinate \((y = 65, 50, \ldots, -70, -85, -100)\) by age (adult vs child), \(F(11,418) = 5.09, P < 0.0001, P_{3} < 0.0005, P_{13} < 0.005, \text{MSe} = 5.78\), indicated that this difference between children and adults was greatest at \(y = 65\) \((26.4)\) and \((21.2)\) for children and adults, respectively. In addition, \(x\) values overall were more lateral in the right hemisphere \((53.2)\) than in the left \((52.1)\), as reflected by a main effect of hemisphere, \(F(1,38) = 149.41, P < 0.0001, P_{3} < 0.0005, P_{13} < 0.005, \text{MSe} = 2.01\). A significant interaction of fixed coordinate by hemisphere (left vs right), \(F(11,418) = 3.27, P < 0.0005, P_{3} < 0.005, P_{13} < 0.05, \text{MSe} = 2.19\), indicated that this difference between right and left hemispheres was greatest at \(y = 65\) \((24.9)\) and \((22.7)\) for right and left hemispheres, respectively and at \(y = -100\) \((26.3)\) and \((24.7)\) for right and left hemispheres, respectively. No other effects in this analysis reached significance.

VARIABILITY OF SULCI

Figure 8 depicts the results from the F tests for the equality of variance that were conducted for each sulcus. Standard deviations are plotted on the y axis as a
function of age. Three of the 10 sulci examined revealed significant differences between children and adults. Overall variance was greater in children than in the adults in the superior frontal sulcus, \( F = 0.58, P < 0.05, P_{10} < 0.5, P_{13} < 0.65 \), and in the central sulcus, \( F = 0.69, P < 0.05, P_{10} < 0.5, P_{13} < 0.65 \). In addition, individual tests at the fixed coordinates revealed that in the central sulcus, variance was greater in children than in adults at fixed coordinate \( x = 35, F = 0.25, P < 0.005, P_{10} < 0.05, P_{13} < 0.07 \), and at fixed coordinate \( x = 40, F = 0.29, P < 0.01, P_{10} < 0.10, P_{13} < 0.13 \). Conversely, overall variance was greater for the adults than for the children in the inferior frontal sulcus, \( F = 1.68, P < 0.05, P_{10} < 0.5, P_{13} < 0.65 \). No other differences between adults and children reached significance.

**Variability of Outer Boundaries**

Figure 9 depicts the results from the \( F \) tests for the equality of variance that were conducted for each outer-boundary section. Standard deviations for adults and children in the left hemisphere are depicted on the left sides of the graphs, and standard deviations for adults and children in the right hemisphere are depicted on the right sides of the graphs. None of the overall comparisons reached significance. However, comparisons of adults and children at the individual fixed coordinates revealed significant differences in all three sections. In the sagittal outer boundary, variance was greater for adults than for children at fixed coordinate \( y = 20 \) in the left hemisphere, \( F = 3.03, P < 0.05, P_{3} < 0.15, P_{13} < 0.65 \). In the coronal outer boundary, variance was greater for adults than for children at fixed coordinate \( z = 35 \) in the left hemisphere, \( F = 3.58, P < 0.01, P_{3} < 0.05, P_{13} < 0.13 \). In the horizontal outer boundary, variance was greater for children than for adults at fixed coordinate \( y = 35 \) in the left hemisphere, \( F = 0.37, P < 0.05, P_{3} < 0.15, P_{13} < 0.65 \).

**Discussion**

In Study 1, we investigated location and variability differences in the coordinates corresponding to 10 sulci and to the outer boundaries of three sections in 7- and 8-year-old children and adult subjects, after transforming all brains into a common anatomic space using identical methods. In the analyses of location differences, three sulci revealed significant effects of age (the superior temporal sulcus, the parieto-occipital sulcus, and the olfactory sulcus). In addition, significant effects of age and hemisphere were observed in all three of the outer-boundary sections. In the analyses of variability differences, variance was greater in children than in adults in the central sulcus, but did not differ in the other sulci. For the outer-boundary sections, variance was greater in children than in adults in the horizontal section, but greater for adults than for children in the sagittal and coronal sections.

Results from the analyses of variability are not entirely in line with previous research suggesting that child brains are more variable than adult brains (e.g., Lange et al., 1997; Muzik et al., 2000). While children were more variable than adults in the superior frontal sulcus, in the central sulcus, and in the horizontal outer-boundary section, adults were more variable than children in the inferior frontal sulcus and in the sagittal and coronal outer-boundary sections. Moreover, 7 of the 10 examined sulci and most of the fixed coordinates in the outer boundary measurements did not exhibit any significant differences in variability between children and adults, once registered in a common stereotactic reference.

The differences observed between child and adult brains in this experiment were small. However, despite the modest size of these differences, significant effects were observed, indicating that the methods used in this study were sensitive enough to detect small differences when present. Thus, results from Study 1 indicate small but systematic differences in the anatomy and anatomical variability of child and adult brains after transformation to a standard stereotactic space.

As noted in the Introduction, the resolution of typical group functional imaging data, after smoothing and normalization, is probably greater than 7 mm. Results from Study 1 indicate that systematic anatomical differences between child and adult brains, while significant, are beneath this resolution. Nonetheless, it is possible that the small differences in anatomy of the size observed might produce false differences in fMRI images of group-wise comparisons. Thus, in Study 2, we examined the extent to which the observed anatomical differences might produce spurious differences in fMRI data.

**STUDY 2**

The effect of anatomical differences in location and variability found in Study 1 on group-comparison fMRI data were assessed using a computer simulation (Bay Zero; Buckner et al., 1998; Burock et al., 1998). Bay Zero simulates a single slice image with parameters under the control of the experimenter, including slice size, response magnitude and location, and level of noise in the image (and response). Because Bay Zero can create images for each of several subjects within multiple groups, simulated responses for each of a group of children and adults could be centered on coordinates from a specific region in Study 1. In other words, the locations and distributions of the responses simulated for each group represented the locations and distributions of points found in the child and adult anatomical measurements, described above. Since the underlying responses (excluding noise terms) plotted
for each member of the groups were the same, if differences were found in the simulated images, they would be due to the anatomical differences between groups rather than the underlying functional response differences between the groups. That is, if functional differences can be found in the group comparison images, then they must be the spurious consequence of simulated anatomical differences, either in location or in variability between the groups.

Method
Selection of Modeled Coordinate
For this study, a single coordinate along one of the measured sulci from Study 1 was chosen. This coordinate was determined by computing the difference, in millimeters, between each measured coordinate in the adults and the corresponding coordinate in the children. The difference scores for each of the measured sulcus coordinates ($n = 45$) and each of the measured outer-boundary coordinates ($n = 66$) are depicted in Figs. 10A and 10B, respectively. After eliminating statistical outliers (difference scores that were greater than 2.5 standard deviations from the mean), the coordinate $z = 40$ along the superior frontal sulcus (in section $y = 25$) had the greatest location difference between children and adults (3.55 mm). Moreover, this coordinate had a relatively large difference in variability between children and adults (2.48 mm). Therefore, the location and variability differences observed for the superior frontal sulcus coordinate $z = 40$ are representative of the largest differences observed between child and adult groups. Differences between children and adults in the $x$ values obtained at this coordinate in Study 1 were modeled in Study 2.

Simulations
Simulated functional images were created for each individual in the child and adult groups to represent each individual location from the superior frontal coordinate described in the preceding section. Functional responses were simulated within a two-dimensional $26 \times 15$ coordinate grid composed of 2.5-mm voxels (see

![FIG. 6. Results from the analysis of the sagittal outer boundary. On the top plotted values in the left hemisphere are displayed as a function of fixed coordinate and age. On the bottom plotted values in the right hemisphere are displayed as a function of fixed coordinate and age. Fixed values are depicted on the x axis and plotted coordinates are depicted on the y axis for each sulcus. Error bars indicate standard errors of the mean. A representative outer boundary from a single adult subject is depicted on the right. Red dots indicate the mean value (across the two plotters) of each plotted coordinate for this subject.](image)
Fig. 11A). The x value (in millimeters) on the superior frontal coordinate for each subject was converted to a voxel value on the horizontal dimension of the grid, and the peak of the response for each subject was centered on this voxel. Peak responses for all subjects were located at the center voxel in the vertical dimension of the grid; hence, response locations differed with respect to the horizontal dimension only. Figure 11A displays the response for a single adult subject (on the right) and a single child subject (on the left). As depicted in this figure, the simulated response falls off in a roughly Gaussian manner such that, with a voxel size of 2.5 mm, the width of the response is 5 mm when the signal drops to 50% of its maximum value (FWHM = 5 mm). Thus, functional images with a 5-mm resolution were simulated. Responses for each subject were generated using the same sequence of events and a signal-to-noise ratio that produced realistically robust Z scores (see Results) in each of the 20-subject groups we examined.

Fig. 11B depicts the locations of the response peaks within the 26 × 15-voxel grid corresponding to locations observed for the adults and children at superior frontal sulcus coordinate z = 40 in Study 1. Only the center voxel in the vertical dimension is shown because, as noted above, the peak responses were always located at the center voxel with respect to the vertical dimension of the grid. White boxes around voxels indicate the location means for each group. Numbers within voxels indicate the number of subjects with peak responses centered on that voxel. Note that because some voxels have more individual subjects centered on them than others, the actual 3.55-mm difference between child and adult groups observed in Study 1 can be simulated. Note also that because variability was greater in the child group than in the adult group, the child group is distributed over more voxels than the adult group.

Six adult groups of 20 subjects each were created by simulating responses at locations that corresponded to locations observed for the adults at superior frontal sulcus coordinate z = 40 in Study 1 (see top of Fig. 11B). Because Bay Zero computes noise in a random manner, each of the six adult groups varied slightly from each other. Similarly, six child groups of 20 subjects each were created. For one of these groups, responses were simulated at locations that corresponded to those observed for the children at superior frontal sulcus coordinate z = 40 in Study 1, putting the center of the response for this group 3.55 mm from the adult.
groups' center location (see bottom of Fig. 11B). For each remaining child group, response locations for each subject were shifted in the horizontal dimension relative to the adult response locations by calculating the displaced value for each subject in millimeters and then converting the millimeter value into a voxel value. In this manner, child groups that differed from the adult groups by different location disparities were created. In particular, child groups were created in which the mean anatomical coordinate differed from the adult mean anatomical coordinate by 0, 2, 5, 10, and 15 mm. These simulated-coordinate offsets are intended to translate to vector distance offsets in three-dimensional atlas space. The locations of the response peaks for child subjects in each of these different disparity groups are shown in Fig. 11C.

Data Analysis

The simulated image data were analyzed using the General Linear Model (GLM; Friston et al., 1994) on a voxel-by-voxel basis, identical to the way that such data are analyzed for actual experiments from our laboratory (e.g., Miezin et al., 2000; Ollinger et al., 2001a,b) and similar to analyses based on statistical parametric mapping (Friston et al., 1995). To define the region in which a response difference might reasonably be found, Z-statistical images representing the main effect of time were derived from the GLM for each of the 6 adult groups and 6 child groups. Based on these images, a "response window" was defined as the extent of voxels in which there was a response with a Z score of 1.96 or greater in any of the 12 groups. This "response window" represented the region of the simulated image in which an actual group difference could be found, and our definition resulted in a window that extended from voxel (6, 8) to voxel (23, 8) within the 26 × 15-voxel image (indicated by the dark rectangle in Fig. 11A). For each Z image, the highest Z value within this response window was identified as the possible response caused by comparison of the groups.

**FIG. 8.** Results from the F test for equal variances for each fixed coordinate in each sulcus. Standard deviation is plotted as a function of fixed coordinate and age.
Each child group was compared to each adult group (adult–child comparison) by performing 36 ANOVAs in which the magnitude of a response across time (at seven time points, reflecting a typical sampling of the hemodynamic response function in fMRI experiments) was a within-subjects independent variable and age group (adult vs child) was a between-subjects variable. These analyses produced Z images representing the interaction of time by age group. In addition, 6 ANOVAs were performed comparing different randomly selected pairings of the adult groups (adult–adult comparison). In these analyses, time (at seven time points) was a within-subjects independent variable and adult group (e.g., adult group 1 vs adult group 2) was a between-subjects variable. Thus in total, we performed 42 different ANOVAs that produced 42 Z images representing the interaction of time × age group (n = 36; 6 ANOVAs at each disparity) and time × adult group (n = 6).

For each of these 42 Z images, the highest interaction Z value within the previously defined response window was recorded. These Z values were then analyzed in a one-way repeated-meaures ANOVA in which “group comparison” (adult–adult vs adult–child (0 mm) vs adult–child (2 mm) vs adult–child (3.55 mm) vs adult–child (5 mm) vs adult–child (10 mm) vs adult–child (15 mm)) was the independent variable.

**Results**

Z images from the six adult groups and the six child groups are shown in the top two rows of Fig. 12. The peak Z value within the response window is indicated next to each image. As expected, due to the greater variance in coordinate location in the child groups than in the adult groups, Z values for the adult groups were higher than values for the child groups overall. Nonetheless, the main effect of time (top two rows in Fig. 12) was highly significant in each group. To assess the location of the functional activation in each group, the center of mass was calculated for each group across three contiguous voxels in the horizontal dimension—

**FIG. 9.** Results from the F test for equal variances for each fixed coordinate in each outer boundary section. Standard deviation is plotted as a function of fixed coordinate, age, and hemisphere.

**FIG. 10.** Difference in millimeters between each measured coordinate in the adults and the corresponding coordinate in the children. The difference scores for each of the measured sulcus coordinates (n = 45) are depicted in A. The difference scores for each of the measured outer-boundary coordinates (n = 66) are depicted in B. The dark, horizontal line indicates the mean of the distribution plus 2.5 standard deviations of that mean, which was the measure that we used to determine outliers. The circled point indicates the difference score for coordinate z = 40 along the superior frontal sulcus, which had the greatest location difference between children and adults (3.55 mm) across all sulci and outer boundary sections, after outliers were excluded.
An illustration of the response placement for the simulations in Study 2. (A) The two-dimensional 26 × 15 coordinate grid, composed of 2.5-mm voxels, in which responses were simulated. The response for a single adult subject is plotted on the right and the response for a single child subject is plotted on the left. Note that the simulated response falls off in a roughly Gaussian manner such that the width of the response is 5 mm when the signal drops to 50% of its maximum value (FWHM = 5 mm). The dark rectangle surrounding voxels 6–23 in the vertical center of the grid depicts the response window across which the center-of-mass was calculated (see Results). (B) The response peaks for the adult and child groups plotted at locations within the 26 × 15-voxel grid that correspond to locations observed for adults and children at superior frontal sulcus coordinate z = 40 in Study 1. (C) The response peaks for child groups plotted at location disparities different from those of the adult group. White boxes around voxels indicate the location means for each group. Numbers within voxels indicate the number of subjects with peak responses centered on that voxel.
the voxel exhibiting the maximum response in the image and one adjacent voxel on each side of this voxel. Thus, centers of mass were calculated across regions that were approximately the size of our image resolution (see Mintun et al., 1989). Voxel values were multiplied by their activation values and the mean of these values across the three voxels was divided by the mean activation for those same voxels. The center of mass of the functional activation within the response window in the child groups generally moved with respect to the center of mass of the activation in the adult groups in accordance with the “anatomical” displacement imposed when creating the groups. For the six adult groups, the centers of mass were located at voxels 17.03, 17.08, 17.95, 17.95, 17.97, and 17.98 (mean location 17.66) in the horizontal dimension. For the child 0 mm group, the center of mass was located at voxel 17.98 (displacement from mean 0.80 mm), in the horizontal dimension. For the child 2 mm group, the center of mass was located at voxel 17.00 (displacement from mean 1.65 mm), in the horizontal dimension. For the child 3.55 mm group, the center of mass was located at voxel 16.03 (displacement from mean 4.08 mm), in the horizontal dimension. For the child 5 mm group, the center of mass was located at voxel 14.99 (displacement from mean 6.68 mm), in the horizontal dimension. For the child 10 mm group, the center of mass was located at voxel 13.01 (displacement from mean 11.63 mm), in the horizontal dimension. And for the child 15 mm group, the center of mass was located at voxel 13.00 (displacement from mean 11.65 mm), in the horizontal dimension.

A representative subset of the Z images showing interactions of time \times age group is shown in the bottom row of Fig. 12. In particular, these images reveal comparisons of an adult group (i.e., group 2) to each of the child groups. The peak Z value within the response window is indicated below each image. Results from the one-way ANOVA assessing differences between the highest Z-statistic values for each of the group comparisons are depicted in Fig. 13. This ANOVA revealed a main effect of group comparison, $F(6,30) = 12.27, P < 0.0001, MSe = 0.38$. T tests comparing the relevant groups indicate that Z values for the adult–adult interactions (2.38), the adult–child 0 mm interactions (2.40), the adult–child 2 mm interactions (2.47), and the adult–child 3.55 mm interactions (2.54) did not differ significantly from one another (all $P > 0.69$). Z values from the adult–child 5 mm group (3.43) were significantly greater than Z values from the adult–
adult group (P < 0.05), the adult–child 0 mm group (P < 0.055), and the adult–child 3.55 mm group (P < 0.05). These values were marginally greater than Z values from the adult–child 2 mm group (P < 0.095). Z values from the adult–child 10 mm group (3.93) were significantly greater than Z values from the adult–adult group, the adult–child 0 mm group, the adult–child 2 mm group, and the adult–child 3.55 mm group (all P < 0.05), but did not differ significantly from the adult–child 5 mm group (P > 0.15). Finally, Z values from the adult–child 15 mm group were significantly greater than Z values in any of the other groups (all P < 0.05).

Discussion

In Study 2, we tested the extent to which observed anatomical differences from Study 1 produced spurious differences in fMRI images, using a computer simulation capable of simulating fMRI data. Spurious differences were assessed by comparing groups of simulated adult subjects to groups of simulated child subjects modeled at different “anatomical” disparities, including the actual disparity observed in Study 1, relative to the adult groups. Results indicate that, when the anatomical disparity between children and adults is below the nominal image resolution, anatomical differences create minimal spurious differences in ≥5-mm resolution functional images. Indeed, the highest Z statistics in the interaction images comparing adults and children at 0, 2, and 3.55 mm disparities were ~2.5 and differed significantly from the highest Z statistics in the interaction images comparing adults and children at 10 or 15 mm disparities (~4.0). Furthermore, Z statistics from the 0, 2, and 3.55 mm disparity interaction images did not differ significantly from each other or from the Z statistics in the adult–adult interaction images.

This set of findings need not be the case; if underlying variability between the two groups was very different, then spurious differences might be found simply because the more variable group averaged together considerably more poorly, producing smaller mean responses at any location. The results of Study 2 indicate that, with anatomical differences in location and variability between children and adults as measured in Study 1, the functional differences produced are not a major contributor to functional differences seen in group comparison images.

GENERAL DISCUSSION

In the present research, the shape and variability differences between 7- and 8-year-old child and adult brains were investigated, after MR images were transformed into a common, adult-derived space (Study 1), and the extent to which these anatomical differences might have produced spurious activation differences was tested in a simulated fMRI experiment (Study 2). Results from Study 1 demonstrate small yet systematic differences in location and variability of child and adult sulci and outer-boundary shapes. However, results from Study 2 indicate that anatomical differences of the magnitude demonstrated in Study 1 should not produce false differences in fMRI data of group-wise comparison. Although the transformation of 7- and 8-year-old children’s brains within the same stereotactic space as adults’ brains results in shape and variability differences in sulci and outer-boundary sections, these differences do not affect functional imaging data substantially, when the resolution of these images is 5 mm or greater.

Results from this work suggest a critical threshold of misregistration, given a 5-mm fMRI image resolution, beyond which spurious functional effects may be seen. Admittedly, it is possible that differences greater than this critical threshold could be found in a region that we did not measure. However, these regions of potential differences are constrained by the distributed nature of our existing measurements, and the potential size of such differences is constrained by the similarity of our sulcus and outer-boundary measures. In other words, the number of widely distributed landmarks measured, and the similarity of the measurements obtained for children and adults, does not leave much “room” for large differences in other unmeasured regions of the brain. Furthermore, as noted in the Introduction, the 5-mm resolution simulated in Study 2 is higher than the actual final resolution that we (and most functional imagers) actually obtain (which is most often greater than 7 mm). Therefore, it is likely
that differences in anatomy of up to 7 mm will not produce spurious functional images.

Critically, this conclusion does not necessarily generalize to children of all ages. As noted earlier, it is not clear whether children younger than 7 years may be normalized effectively within an adult-derived space. Indeed, when Muzik and colleagues (2000) compared the contours of brain images from a group of healthy adults to two age groups of children with medically intractable epilepsy [a younger group (ages 2–6 years) and an older group (ages 7–14 years)], they observed greater differences between the contours of the younger group of children and the adults than between the older group of children and the adults. Moreover, work by Courchesne and colleagues (2000) suggests that the ratio of gray to white matter does not begin to approximate that of adults until around age 7 years. Certainly, more work comparing younger children’s brains (below 7 years) to adult brains is needed before similar stereotactic approaches should be applied to that group.

In addition, our conclusions apply only to normal populations of adults and children. Nonetheless, the method described in the present studies could be used to compare normal and nonnormal populations and assess the consequences that anatomical differences between these populations may have for transformation of these groups into a common space. Studies of nonnormal populations (both child and adult) could benefit immensely from precise knowledge about the extent to which normal and nonnormal brains may be effectively transformed into the same space.

To be clear, this study was in no way intended to exhaustively characterize the anatomical variability in human brain development. Instead, the explicit purpose of the present research was to assess the possibility of using specific spatial normalization techniques to compare regions of functional activation in school-aged children and adults. The methods chosen reflect this stated objective. We find that, despite reservations expressed in the nascent developmental fMRI literature, utilization of a standard stereotactic space for studies of developmental cognitive science is feasible when accepting functional imaging information with resolution greater than 5 mm. Moreover, the methods described in this work are easy to implement, allowing our procedure to be used by many imaging groups without the need for extensive algorithmic development.

The value in being able to transform pediatric and adult brains to the same space is substantial because it allows direct statistical comparisons of groups of subjects. In recent work from our group on a series of language tasks, we have taken advantage of the findings from the present study and transformed functional imaging data from both children and adults into the same stereotactic space. While many brain regions show essentially similar activation patterns, the use of direct comparison has enabled the identification of isolated regions of systematic functional difference between the age groups (Schlaggar et al., 2002). For studies of functional neuroimaging directed at development, such an approach greatly facilitates the precision with which functional anatomical similarities and differences can be described and interpreted.

ACKNOWLEDGMENTS

B.L.S. is a scholar of the Child Health Research Center of Excellence in Developmental Biology at Washington University School of Medicine (HD01487). Other support for this research was provided by the McDonnell Center for Higher Brain Function (B.L.S.) and by the National Institutes of Health, NSADA (B.L.S.) and NS32379 (S.E.P.). In addition, we thank Rebecca Coalson and Rebecca Dunlap, for their assistance in analyzing and plotting sulci. Portions of this research were reported at the Annual Meeting of the Cognitive Neuroscience Society, New York, New York (March 2001).

REFERENCES


