



ACADEMIC  
PRESS

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

SCIENCE @ DIRECT®

NeuroImage

NeuroImage 19 (2003) 16–28

[www.elsevier.com/locate/ynimg](http://www.elsevier.com/locate/ynimg)

## Comparison of functional activation foci in children and adults using a common stereotactic space

Hyunseon Christine Kang,<sup>a</sup> E. Darcy Burgund,<sup>a</sup> Heather M. Lugar,<sup>a</sup> Steven E. Petersen,<sup>a,b,c,e</sup> and Bradley L. Schlaggar<sup>a,b,d,\*</sup>

<sup>a</sup> Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110, USA

<sup>b</sup> Department of Radiology, Washington University School of Medicine, St. Louis, MO 63110, USA

<sup>c</sup> Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO 63110, USA

<sup>d</sup> Department of Pediatrics, Washington University School of Medicine, St. Louis, MO 63110, USA

<sup>e</sup> Department of Psychology, Washington University, St. Louis, MO 63130, USA

Received 22 June 2002; accepted 22 November 2002

### Abstract

The development of methods allowing direct comparisons between child and adult neuroimaging data is an important prerequisite for studying the neural bases of cognitive development. Several issues arise when attempting to make such direct comparisons, including the comparability of anatomical localization of functional responses and the magnitude and time course of the hemodynamic responses themselves. Previous results suggest that, after transformation into a common stereotactic space, anatomical differences between children (ages 7 and 8) and adults are small relative to the resolution of fMRI data. Here, we investigate whether time courses (BOLD responses) and locations of functional activation foci show similarities as well. Event-related fMRI was performed on 16 children (ages 7 and 8) and 16 adults, who pressed buttons in response to a visual stimulus. After transforming images into Talairach space, the coordinates of four consistent activations in each hemisphere were determined for each subject: two foci in the sensorimotor cortex, one focus in the visual cortex, and one focus in the supplementary motor area (eight activations in total). In seven foci, time courses were similar between children and adults, and peak amplitudes of time courses were comparable in all eight foci. There were negligible between-group differences in location of all foci. Variability of activation location was statistically similar in the two groups. In voxelwise group comparison images, minimal differences were found between children and adults in visual and motor cortex regions. The small differences in time courses and locations of activation foci between child and adult brains validate the feasibility of direct statistical comparison of these groups within a common space.

© 2003 Elsevier Science (USA). All rights reserved.

### Introduction

The advent of functional magnetic resonance imaging (fMRI) has opened a new era in the study of human brain development. Previously, such research was limited by the low occurrence of autopsies in pediatric populations and the ethical problems associated with imaging normal children using ionizing radiation modalities such as computerized

tomography, positron emission tomography (PET), and single photon emission computerized tomography (SPECT). PET and SPECT studies performed on clinical pediatric patients, while informative, raise questions about the generalizability of the results to normal healthy children. FMRI, on the other hand, is non-ionizing, noninvasive, safe, and repeatable and therefore provides a means to address cognitive neuroscientific issues in normally developing children (Booth et al., 1999; Bunge et al., 2002; Casey et al., 1995, 1997; Gaillard et al., 2000; Gaillard et al., 2001b; Klingberg et al., 2002; Lee et al., 1999; Luna et al., 2001; Martin et al., 1999; Nelson et al., 2000; Schlaggar et al., 2002; Thomas et al., 1999).

\* Corresponding author. Department of Neurology, Washington University School of Medicine Campus Box 8111, 660 South Euclid Avenue, St. Louis, MO 63110.

E-mail address: [schlaggar@neuro.wustl.edu](mailto:schlaggar@neuro.wustl.edu) (B.L. Schlaggar).

In functional neuroimaging studies, spatial normalization is a powerful tool that allows direct voxelwise comparison of data sets between different subjects and subject groups (Fox et al., 1985a). Spatial normalization refers to the process of transforming an individual subject's image to match a standard brain or brain template. After all brains have been transformed into a common stereotactic space, researchers are able to perform between-subject comparisons and report findings in standardized coordinates.

The ability to apply similar stereotactic approaches to neuroimaging data from developmental populations would allow children at various developmental stages to be directly compared with each other and with adults. Direct comparison would greatly enhance the sensitivity and reliability of fMRI to draw inferences about age-related changes in the developing brain.

As a step in the development of such an approach to the comparison of adult and child neuroimaging data, this study explores the feasibility of using an adult-derived template for spatial normalization of children's brains. Two conditions must be met before adult and child brains can be directly compared at the voxel level.

First, since fMRI relies upon the blood oxygenation level-dependent (BOLD) contrast signal as an indirect measure of cerebral activity (Ogawa et al., 1990), a prerequisite of direct comparisons between children and adults is that the two groups have physiologically similar BOLD responses. If BOLD signals were commonly seen to have different time profiles, or greater variance, in children than in adults, it would be difficult to draw conclusions about group differences using fMRI methods.

Second, spatial normalization should affect both groups similarly, so that "functional differences" are not spuriously produced by the process of spatial normalization itself. Previously, we have addressed the question of whether systematic differences in brain anatomy can be found between children (ages 7 and 8) and adults following the spatial normalization procedure (Burgund et al., 2002). After transformation to a common space, differences in location and variability of selected sulci and overall brain outlines in three dimensions were found to be small ( $< 4$  mm) relative to the effective resolution of group fMRI images. As part of this study, computer simulation was used to assess the potential of (a range of) anatomical differences to produce spurious effects in functional imaging data. On the basis of simulated fMRI data, it was concluded that the anatomical differences in location and variability that were found would not produce spurious functional differences.

Both anatomical and functional differences between groups should be interpreted in the context of the resolution of fMRI data. Commonly, fMRI images are acquired at a resolution of approximately  $3 \times 3$  mm in plane, with slice thickness ranging from 3 to 8 mm. The raw data are sometimes smoothed by varying amounts. Resampling during transformation to a standard space also smoothes the images. This results in the effective resolution of typical func-

tional neuroimaging data being greater than 5 mm (and probably at least 8 mm). Differences in location and variability between adult and child neuroimaging data that are below the resolution of the image should not hinder researchers from transforming data to a common space. For this reason, a between-group difference of approximately 4 mm in the location of one sulcus in the previous study did not prevent us from concluding that transformation to a common stereotactic space was feasible for child and adult brains.

In the present study, we extend our previous work to compare actual fMRI data in children (ages 7 and 8) and adults, after transformation into a common stereotactic space. As indices of functional variability, time courses and locations of functional activation foci, and the variability of these responses, were analyzed in eight foci (two in sensorimotor cortex, one in SMA, and one in visual cortex, in each hemisphere) in each subject. The hypothesis was that, using a simple visuomotor task, the temporal profile of time courses and the location and variability of functional activations would not be different in sensorimotor cortex and visual cortex. If large between-group differences in time course or location of activation foci were found, this would serve to discourage direct statistical comparison between children and adults. Alternatively, the presence of similar responses in these cortical processing regions would support the feasibility of using a common stereotactic atlas for transformation of child and adult brains.

## Methods

### *Subjects*

Sixteen 7- and 8-year-old children (8 female; mean age  $8.1 \pm 0.6$ ; range 7–8; 2 left-handed) and 16 adults (8 female; mean age  $26.4 \pm 4.2$ ; range 20–35; all right-handed) participated in the study. All subjects were screened with a questionnaire to ensure that they had no history of neurological problems or drug abuse. Pediatric subjects made an additional visit to the lab (before the actual scan) during which they were examined by a pediatric neurologist (B.L.S.), completed a detailed health questionnaire to assess normal development, and were acclimatized to the MRI environment in a "mock" scanner. During this session, they also practiced the task in a behavioral testing room. Informed consent was obtained from all adult subjects and parents of pediatric subjects, and assent was obtained from pediatric participants, in accordance with the guidelines and approval of the Washington University Human Studies Committee. All subjects were paid for their participation. Data from 8 additional subjects (1 adult, 7 children) were not used due to movement artifacts or incomplete data acquisition.

### *Imaging procedures*

MRI data were acquired using a Siemens 1.5-T Vision scanner (Erlangen, Germany) with a standard circularly polarized head coil. A pillow and a thermoplastic face mask were used to minimize head movement. Headphones dampened scanner noise to less than 70 dB and enabled communication with subjects. A Power Macintosh computer (Apple, Cupertino, CA) and Psyscope software (Cohen et al., 1993) were used for stimulus display and recording of responses from a fiberoptic key-press device held in the subject's hands. An LCD projector (Epson Model 500) was used to project stimuli onto a screen at the head of the bore, which the subjects viewed through a mirror attached to the coil.

High-resolution structural images were obtained using a sagittal MP-RAGE three-dimensional T1-weighted sequence (repetition time, 9.7 ms; echo time, 4 ms; flip angle, 12°; inversion time, 300 ms; voxel size, 1 × 1 × 1.25 mm).

Functional images were acquired using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast (e.g., T2\*, repetition time, 2.5 s; T2\* evolution time, 50 ms; flip angle, 90°; voxel size, 3.75 × 3.75-mm in-plane resolution). During each scan, 88 sets (frames) of 16 contiguous interleaved 8-mm-thick axial slices were acquired parallel to the plane transecting the anterior and posterior commissures (AC-PC plane). This plane was defined with an automated program utilizing a low-resolution MP-RAGE image. The first 4 frames in each run were discarded to allow stabilization of longitudinal magnetization.

Each functional run lasted approximately 3.67 min (88 acquisitions, 1 acquisition every 2.5 s). Between 5 and 11 runs were acquired in each subject. Since all analyses involved identification of regions on an individual basis, we felt that it was appropriate to use all available data from each subject in defining functional activation foci. Only 1 run in one child subject was excluded from further analyses, due to a large number of response omissions.

### *Behavioral paradigm*

A relatively simple visuomotor task was chosen for study in order to minimize developmental differences in task performance strategies that might lead to differences in functional activation. This task is known to generate highly reproducible activation in sensorimotor and visual cortex in adults (Miezin et al., 2000). Subjects pressed a button at the onset and offset of a visual stimulus presented for 1.26 s. The visual stimulus was a radial counterphase flickering checkerboard subtending ~3° of the visual field surrounding the fovea. Right and left index fingers were used for onset and offset, counterbalanced across subjects. An event-related procedure was used, in which stimulus presentation was jittered throughout the functional run. Gaps (fixation-only frames) were randomly interspersed with stimulus trials so that, on each frame, there was a 50% probability of a

gap and 50% probability of a visual stimulus. This resulted in a distribution of gaps that was near exponential, with long gaps relatively underrepresented. There were approximately 40 stimulus presentations per each 88-frame run. Stimulus onset was synchronized to the beginning of a frame. Subjects were instructed to fixate their gaze on a fixation cross-hair that was presented in the center of the checkerboard stimulus and remained on the screen for the duration of the run.

### *Spatial normalization*

Spatial normalization 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). This method differs from that used in SPM (when affine normalization is chosen as an option) only in the image used as the atlas-representative target (Evans et al., 1994). The common strategy was first described by Collins and colleagues (1994) in application to positron emission tomography. Our atlas-representative target was prepared by 12-parameter affine coregistration of MP-RAGE images representing a completely independent group of 12 neurologically normal young adults (ages 18–35). The composite target 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. The transforms were used to create the atlas representative image by resampling (to 2-mm cubic voxels) and averaging using one interpolation per subject. Atlas-transformed data were then resampled to 1-mm cubic voxels.

### *Data preprocessing*

BOLD (functional) data from each subject were preprocessed to remove noise and artifacts. This involved (1) removal of a single pixel spike caused by signal offset and its value replaced with the local pixel average, (2) temporal realignment (using sinc interpolation) of all slices to the midpoint of the first slice, to correct for differences in the acquisition time of each individual slice, (3) slice-by-slice normalization to correct for changes in signal intensity introduced by the acquisition of interleaved slices, (4) correction for movement within and across runs using a rigid-body rotation and translation algorithm (Snyder, 1996), and (5) reslicing by three-dimensional cubic spline interpolation (Hajnal et al., 1995). The functional images were then registered to the reference brain using the alignment parameters derived for the structural scans.

### *Movement analysis*

The rigid-body translation and rotation algorithm (Snyder, 1996) outputs the adjustments required for realignment

of each image at each MR frame. This information can be used as a measure of head movement in six dimensions: translations and rotations in the  $x$ ,  $y$ , and  $z$  planes. For each run in each subject, average head position was computed for each of the six dimensions. The root mean squares (rms) of the difference between this average and the actual head position during each frame provides a measure of average movement in that dimension during one run. The total movement (translation and rotation) during one run was calculated as the rms of the three translation parameters and the three rotation parameters. The total movement was averaged across all runs in a subject to acquire per-individual movement measures.

### Data analysis

To detect task-related activations, preprocessed data were analyzed using an implementation of the general linear model (GLM) (Friston et al., 1994; Josephs et al., 1997; Ollinger et al., 2001; Worsley and Friston, 1995; Zarahn et al., 1997) in which no assumptions were made about the shape of the hemodynamic response. The design of the GLM included the seven MR frames following presentation of the stimulus; thus, the hemodynamic response function was modeled over a period of 17.5 s. All trials (including error trials) were included in the analysis.

In order to identify activated regions, omnibus  $F$  statistics were computed from the time courses using the extra sum of squares principle (Beck and Arnold, 1977). This method allows one to determine significance levels without making any assumptions about the shape of the hemodynamic response. Thus, the  $F$  statistic map represents the amount of time series variance in each voxel that can be accounted for by the GLM.  $F$  statistic images were generated for each subject and transformed into the standardized stereotactic space as discussed above (Talairach and Tournoux, 1988).

### Selection of activation foci

Activations in visual cortex and sensorimotor cortex had the highest peaks on  $F$  statistic images (i.e., were most reliable). From the unsmoothed  $F$  statistic images, a three-dimensional search program (Mintun et al., 1989) was used to identify the coordinates of active peak voxels in bilateral sensorimotor cortex, supplementary motor area (SMA), and visual cortex. This program searches for activation peaks in the image and will find the center-of-mass (in  $x$ ,  $y$ , and  $z$  stereotactic coordinates) and average  $F$  statistic of activated voxels within a specified radius of the peak. Since the resolution of the activation image is close to 8 mm (BOLD images are acquired at a resolution of  $3.75 \times 3.75$  mm in-plane, with 8-mm slice thickness), a sphere with a 4-mm radius was used to search for peaks. Adjacent peaks less than 8 mm (vector distance) away were ignored. Subsequent analyses of the location of activation foci were performed

with the coordinates of the center-of-mass of this sphere. For time course analyses, the MR response during each of the seven frames was averaged among the voxels in this 4-mm-radius sphere. Selection of foci was done on an individual subject basis, as the purpose of the present study was to examine the intersubject variability of fMRI data.

The peak-search algorithm found multiple activations in visual cortex, sensorimotor cortex, and SMA. However, in order to study variability of fMRI activations, it is important that the “same” activation be compared in all subjects. Therefore, a protocol was developed to consistently choose the “same” functional activation for each region in each subject. To that end, underlying brain anatomy was used as the basis for selection of activation foci. First, an anatomical landmark (a particular sulcus or gyrus) was identified in each region on the structural MP-RAGE images. Then, omnibus  $F$  statistic images were overlaid onto the anatomical images. Using the output of the peak-search algorithm, the coordinates of the activation located on or nearest to the anatomical landmark were used for further analyses. Four activations were chosen to be plotted in each hemisphere in all subjects (a total of eight activation foci).

In the sensorimotor cortex (Fig. 1A), the “omega”-shaped hand region of the central sulcus was identified on a transverse section of the brain, and two activation foci found on the medial and lateral arms of the “omega”. The omega-shaped knob corresponds to the contralateral hand representation in primary motor and somatosensory cortex (Sastre-Janer et al., 1998; Yousry et al., 1997). In many cases, the medial and lateral activation foci could be found on the same section; in other cases, the omega was traced to more superior or inferior sections so that both activations could be identified.

For the SMA activation (Fig. 1B), the paracentral sulcus (which constitutes the anterior border of the paracentral lobule) was found on the medial wall (on sagittal section) and gyri anterior to this were labeled g1 and g2. The activation located on g2 or the g1/g2 border was used in the analysis; in the few cases when there was no activation on g2, the activation on g1 was used (2 children, 1 adult). Except for 2 child subjects (whose activations were located on coronal plane  $Y = 1$ ), all SMA activations were located posterior to the coronal plane of the anterior commissure, in accordance with known boundaries of human SMA proper (Picard and Strick, 1996). In 15 subjects (6 adults, 9 children) in whom the left and right SMA activations were indistinguishable (located at the midline, less than 8 mm apart), the same coordinates were used for both right and left SMA analyses.

For the visual cortex (Fig. 1C), sagittal and coronal sections of the brain were examined to identify the lateral occipital sulcus (LOS) at the occipital pole, located lateral and superior to the calcarine sulcus. The activation on or closest to the posterior tip of the LOS was plotted. This activation was chosen (rather than one on the calcarine sulcus, for example) because it was more consistently identifiable on a single-subject basis.

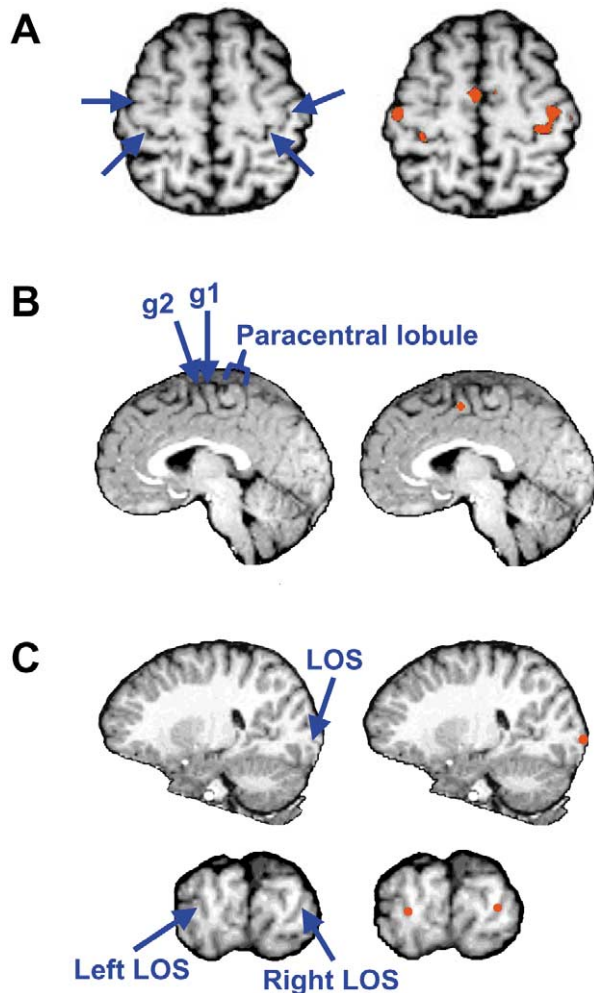


Fig. 1. Selection of activation foci. Anatomical landmarks are identified on three representative brains on the left panels, with activation foci (red dots) overlaid on the right. (A) Sensorimotor cortex (transverse section  $Z = 54$ ). The “omega”-shaped hand area was first identified on an anatomical image (left). Arrows point to lateral and medial arms of the omega. Activation images were then overlaid on the anatomical images (right) and activation foci located on the medial and lateral arms of the omega were chosen for further analyses. The SMA can also be found on this section (on medial wall). (B) Supplementary motor area (SMA). Sagittal anatomical sections near the midline (such as this section  $X = -3$ ) were examined for the paracentral sulcus, which constitutes the anterior border of the paracentral lobule (left). Preceding gyri were labeled g1 and g2 (arrows). Activation images were overlaid on anatomical images (right) and activations located on g2 were used in subsequent analyses. (C) Visual cortex. Sagittal (top) and coronal (bottom) sections were examined for the lateral occipital sulcus (LOS; arrows) at the occipital pole. This sulcus is located lateral and dorsal to the calcarine sulcus. The activation on or closest to the posterior tip of the LOS was selected for further analyses (right panels). The sections depicted in this panel are  $X = 23$  and  $Y = -95$ .

### Statistical analyses of activations

After selection of activation foci in each region and in each subject, average time courses for each spherical activation were subjected to a repeated measures ANOVA (Group, adult or child; MR frame, 1–7) in order to examine differences in the temporal profile of the time courses be-

tween children and adults. A separate ANOVA (Group, adult or child) was performed on the peak amplitudes from each time course to determine differences in maximum percentage signal change values between children and adults.  $F$  tests for the equality of variances were used to assess differences in the variability of peak amplitudes of time courses across the two groups.

To examine group differences in average location of activations, the stereotactic coordinates of activation foci were used to perform multivariate analyses of variance (MANOVA) for each of the eight foci. The dependent variables were  $x$ ,  $y$ , and  $z$  coordinates, and Group (adult or child) was the between-subjects independent variable. To measure the variability of activation location in the two groups,  $F$  tests for the equality of variances were performed for each coordinate in each region. As before, coordinate was the dependent measure in all analyses.

### Voxel-by-voxel ANOVA

All analyses up to this point were performed on regions defined individually. Pragmatically, many fMRI studies use voxelwise group comparisons to analyze group differences or to define regions of interest. In order to confirm that transformation to a common template is a useful technique for direct comparison of adult and child fMRI data (i.e., it does not produce spurious between-group differences), we next performed a whole-brain voxel-by-voxel ANOVA with Group (adult or child) and Time (MR frame 1–7) as the two factors. The resulting images were corrected for the large number of comparisons using the Monte Carlo method (24 contiguous voxels with  $Z$  score  $> 3.5$  are needed to achieve  $P < 0.05$ ). If there are few functional differences between child and adult brains transformed into a common space, there should be a lack of statistical significance in the Group  $\times$  Time interaction image.

## Results

### Behavioral results

Behavioral performance data were analyzed for response times and errors. Reaction times for “onset” and “offset” button presses were analyzed with two-tailed two-sample  $t$  tests. “Onset” response times were significantly longer in the children (595 ms) than in the adults (351 ms) ( $T_{30} = 5.8$ ,  $P < 0.00001$ ), but there was no significant difference in the “offset” button-press response times (children, 720 ms; adults, 650 ms) ( $T_{29} = 1.3$ ,  $P > 0.05$ ). This may be due to the fact that the flickering checkerboard stimulus was presented for a fixed duration of 1.26 s, and therefore its offset was predictable. “Offset” reaction times for one child were unavailable due to technical problems.

Button-press errors were divided into “onset” omissions, “offset” omissions, and depression of inappropriate buttons.

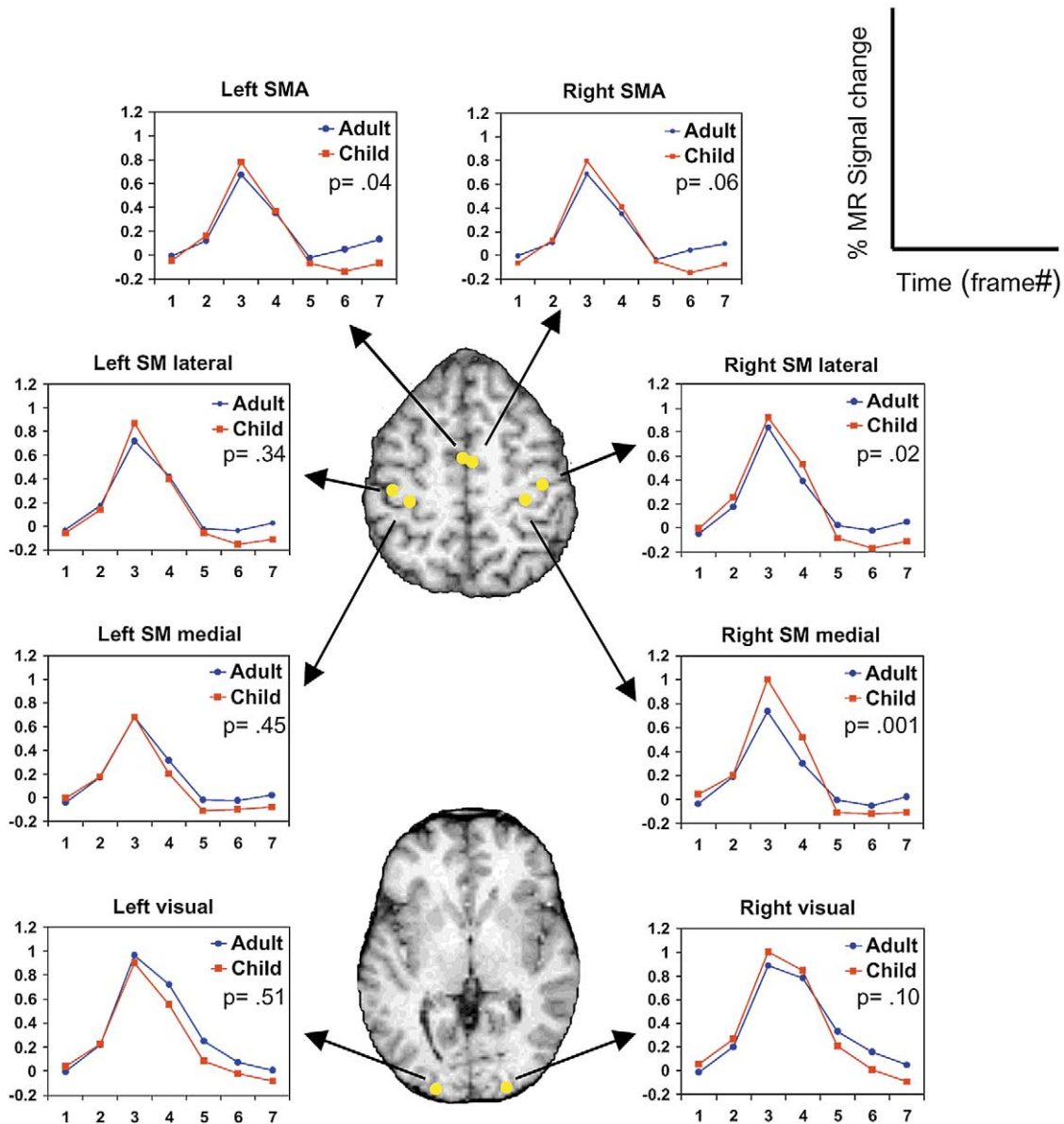


Fig. 2. Results from the time course analyses. Average time courses in each region are depicted as a function of time and group (adult vs child). Each MR frame is 2.5 s.  $P$  values from the repeated-measures ANOVA on frames 1–7 are shown next to each time course.

Percentages of errors were calculated for each individual and two-tailed two-sample  $t$  tests performed on the two groups. Omissions at the onset of the flickering stimulus were few in both child and adult subjects (median percentages of omissions, 0.5% for child subjects and 0% for adult subjects), and there was no significant difference in their percentages ( $T_{30} = 0.26$ ,  $P > 0.05$ ). Omissions at the offset of the flickering checkerboard were significantly more frequent in child subjects (median percentage of “offset” omissions, 6.8%) than in adult subjects (median percentage of “offset” omissions, 0.2%) ( $T_{29} = 2.4$ ,  $P < 0.05$ ). In addition, child subjects made a greater number of incorrect responses, e.g., pressing the “onset” button at the offset of the flickering stimulus and vice versa ( $T_{30} = 5.5$ ,  $P < 0.00001$ ) (median percentages of incorrect responses, 1.5% for chil-

dren and 0% for adults). One possible source of inaccuracy in the numbers of omissions is the fact that the button-press device used in the scanner was somewhat stiff, which may have resulted in incomplete depression of buttons by child subjects, and our inability to record responses.

#### Spatial normalization

In the spatial normalization procedure, individual MP-RAGE images are warped to an atlas representative target. Eta ( $\eta$ ) is the correlation coefficient, and  $\eta^2$  is a measure of the variance accounted for by the transform. Eta values above 0.985 are considered satisfactory. Average  $\eta$  resulting from the transform was similar in the two groups (0.9899 for adults and 0.9870 for children), although, due to

Table 1  
Results from repeated measures ANOVA on time courses

Region		Frames 1–7 ANOVA		Frames 1–5 ANOVA	
		<i>F</i> statistic	<i>P</i> value	<i>F</i> statistic	<i>P</i> value
SMA	Right	2.044	0.062	0.589	0.671
	Left	2.177	0.047	0.628	0.643
Sensorimotor medial	Right	4.890	0.001	3.879	0.005
	Left	0.970	0.447	0.912	0.459
Sensorimotor lateral	Right	2.669	0.017	1.204	0.313
	Left	1.148	0.337	0.741	0.566
Visual cortex	Right	1.795	0.103	0.942	0.442
	Left	0.872	0.516	0.976	0.423

the small variance, the means were significantly different ( $T_{30} = 5.6$ ,  $P < 0.00001$ ).

### Movement analysis

Measures of head movement were obtained from the output of the rigid-body translation and rotation algorithm (Snyder, 1996). Translations and rotations in the  $x$ ,  $y$ , and  $z$  dimensions were averaged across frames, and total rms linear and angular precision measures calculated for each BOLD run. These values were then averaged for all runs within a subject, and two-sample  $t$  tests performed on the two groups. Based on this parameter, child subjects had significantly more head movement on average than adult subjects ( $T_{30} = 3.7$ ,  $P < 0.001$ ), although average rms values for both groups were well under 1 (0.41 for children and 0.24 for adults). A total movement value of 1.5 was predefined as the criterion for exclusion of single runs from further analyses; however, no individual runs were excluded on the basis of movement parameters. These results are in agreement with other studies showing that children generally have more head motion in their data than adults (Poldrack et al., 2002; Schlaggar et al., 2002; Thomas et al., 1999).

### Time course analyses

Results from the time course analyses are reported in Table 1 and depicted in Fig. 2. Since eight activation foci were compared for the two groups, a Bonferroni-corrected  $P$  value of 0.00625 was used as the threshold for significance.  $P$  values that were nonsignificant before correction are reported as such ( $P > 0.05$ ), those that were nonsignificant after correction are reported as  $P > 0.00625$ , and those that were significant after correction for multiple comparisons are reported as  $P < 0.00625$ .

Repeated measures ANOVA across the seven time points (frames) showed that, for seven activation foci (bilateral visual, bilateral SMA, left sensorimotor medial and lateral, and right sensorimotor lateral), there were no significant differences between the average timecourses for adults and children (all  $P$ s  $> 0.00625$ , five  $P$ s  $> 0.05$ ) (Table 1). A significant time course by age interaction was

found in the right sensorimotor medial activation ( $P < 0.00625$ ). In a separate repeated measures ANOVA on frames 1–5 of each time course (emphasizing the time points of maximal change), seven activation foci showed no differences between adults and children (all  $P$ s  $> 0.05$ ); time courses in the right sensorimotor medial activation remained significantly different between children and adults ( $P < 0.00625$ ) (Table 1).

To determine whether peak amplitudes of the time courses were different between children and adults (whether the time course by age interaction in the right sensorimotor medial activation was due to differences in time course magnitude), a separate ANOVA was performed using the maximum percentage signal change value among the seven frames. None of the activation foci showed a significant difference between children and adults in maximum percentage signal change (all  $P$ s  $> 0.05$ ). These results are in accord with other studies also showing that average MR signal intensity is not different between children (ages 8–10) and adults (Thomas et al., 1999).

$F$  tests for the equality of variances were conducted on the peak amplitudes of each time course. No significant effects of age were observed in any of the eight foci (all  $P$ s  $> 0.05$ ).

### Mean locations of foci

Groupwise average locations of activation in each region are reported in Table 2, with the corresponding standard deviations. Results from MANOVA on each region are reported in Table 3. As before, a Bonferroni-corrected  $P$  value of 0.00625 was used as the threshold for significance.

Results from analyses of the bilateral sensorimotor cortex and bilateral SMA foci are depicted in Fig. 3. Mean coordinates  $\pm$  SD are overlaid on two representative brain outlines. On the coronal view, the  $y$  axis has been collapsed so that all six foci can be represented on a single slice, in order to facilitate visual comparison. On the horizontal view, the  $z$  axis has been collapsed for the same reason. Locations of activations were not statistically different between adults and children in these six foci (right sensorimotor medial, right sensorimotor lateral, left sensorimotor medial, left sensorimotor lateral, right SMA, and left SMA) (all  $P$ s  $> 0.05$ ).

Table 2  
Mean locations of activation foci and their standard deviations along *x*, *y*, and *z* axes

Region		Mean location (mm) (Talairach coordinates)			Standard deviation (mm)		
		<i>x</i>	<i>y</i>	<i>z</i>	<i>x</i>	<i>y</i>	<i>z</i>
Left SM lateral	Adult	−41	−24	51	3.0	4.4	4.4
	Child	−41	−24	50	2.4	3.8	2.9
Right SM lateral	Adult	40	−21	52	4.0	4.3	3.7
	Child	38	−21	52	3.7	4.0	4.6
Left SM medial	Adult	−31	−31	54	4.8	3.6	5.5
	Child	−31	−30	50	3.5	4.0	3.4
Right SM medial	Adult	30	−29	54	4.6	3.3	4.2
	Child	29	−28	53	3.8	4.4	3.7
Left SMA	Adult	−4	−8	53	3.5	3.8	5.6
	Child	−2	−8	52	3.8	5.3	5.3
Right SMA	Adult	2	−9	53	3.8	4.1	4.6
	Child	3	−8	53	3.5	5.3	5.3
Left visual	Adult	−19	−96	−3	3.1	3.3	4.6
	Child	−21	−100	−4	4.1	2.7	3.5
Right visual	Adult	23	−96	1	3.0	3.8	4.9
	Child	24	−97	1	3.7	4.0	5.7

*Note.* The *x*, *y*, and *z* coordinates are in a standard stereotactic space (Talairach and Tournoux, 1988) in which positive values refer to regions right of (*x*), anterior to (*y*), and superior to (*z*) the anterior commissure.

Results from analyses of the visual cortex activations are depicted in Fig. 4. Mean coordinates  $\pm$  SD are overlaid on two representative brain outlines. Again, *z* coordinates have been ignored on the horizontal view, and *y* coordinates ignored on the coronal view. Locations of foci were not statistically different between adults and children in both right ( $P > 0.05$ ) and left ( $P > 0.00625$ ) visual cortex activations, although the difference in the location of the left visual cortex activation (vector distance  $\sim$  4 mm) approached significance ( $P = 0.008$ ). This difference was mainly along the *y* axis, as can be seen in Fig. 4A.

#### Variability of foci

*F* tests for the equality of variances showed that, for all eight foci, there were no significant differences in the variability of activation location between children and adults (all  $P$ s  $> 0.05$ ). This can also be predicted from the visual similarity of the error bars in Fig. 3 and 4. Pooled mean standard deviation values for all axes across all eight regions were 4.18 and 4.04 mm for adults and children, respectively.

Intersubject variability of functional areas (as measured by standard deviations in millimeters along each axis) has been reported to be in the range of 3–7 mm, for adult visual cortex (Belliveau et al., 1991; Fox et al., 1986; Hasnain et al., 1998), motor cortex (Ramsey et al., 1996), and somatosensory cortex (Fox et al., 1987; Schlaug et al., 1994). These findings are in agreement with our results for both children and adults, which were 2.4–5.7 mm.

#### Voxel-by-voxel ANOVA

The voxel-by-voxel Group  $\times$  Time interaction image is shown in Fig. 5. No differences were detected between child

and adult brains in most regions of the brain, including bilateral visual cortex, bilateral SMA, and left sensorimotor cortex. Interestingly, there was a differential response across time in the right sensorimotor cortex (Fig. 5; arrow), about 5 mm (vector distance) away from the right SM medial activation used in our analyses. This focus had the same pattern of time courses as the right SM medial focus, except that the peaks of both child and adult average time courses were smaller in amplitude. Thus, our results from the individual-based analyses and the voxelwise analysis were largely comparable.

## Discussion

### Major findings

Among the eight activation foci examined, time courses were similar between children and adults in seven foci, and in the eighth, there was no difference in peak amplitude.

Table 3  
Results from MANOVA on locations of activation foci

Region		MANOVA ( <i>P</i> value)
SMA	Right	0.92
	Left	0.53
Sensorimotor medial	Right	0.80
	Left	0.16
Sensorimotor lateral	Right	0.62
	Left	0.99
Visual cortex	Right	0.26
	Left	0.008

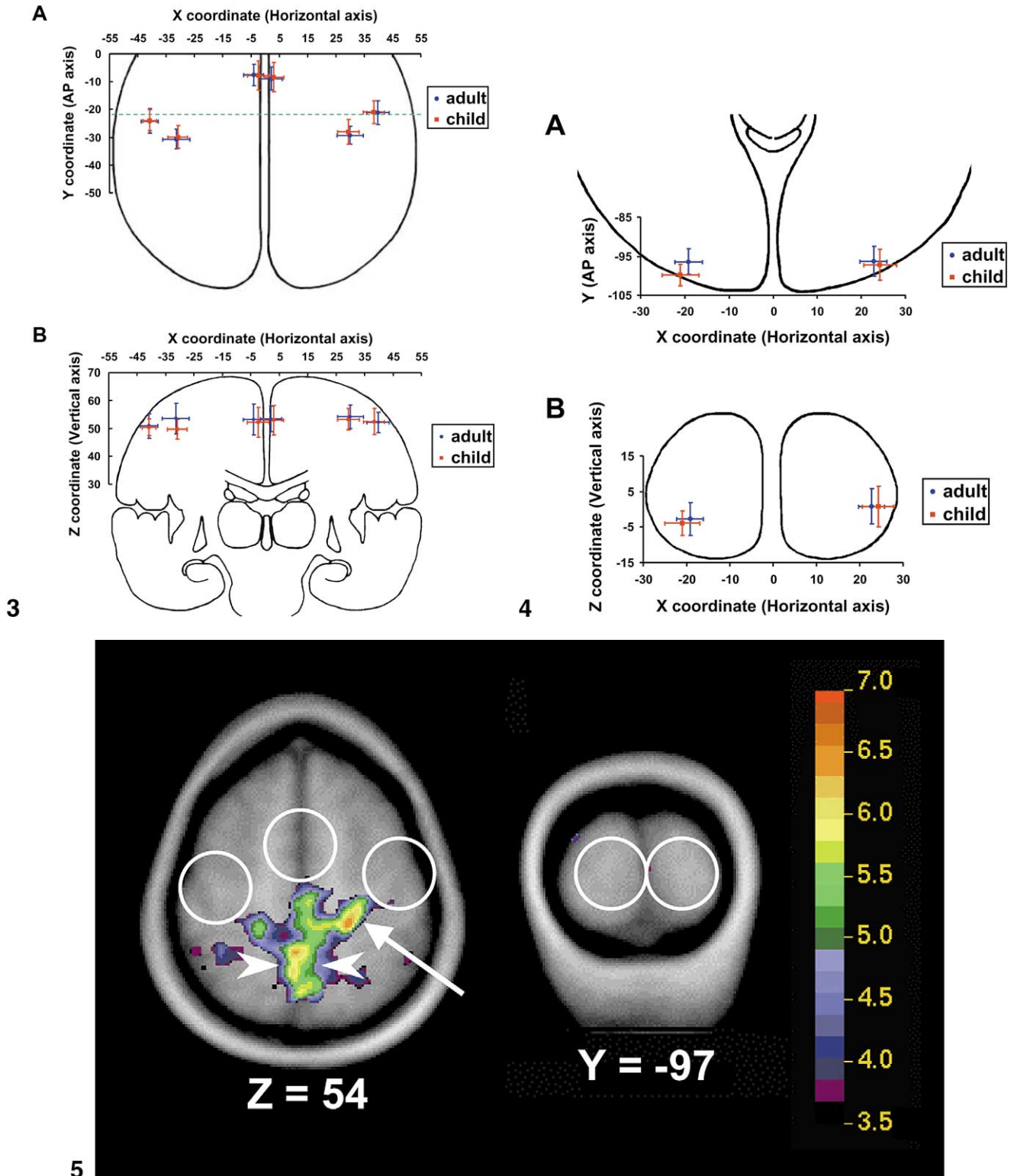


Fig. 3. Results from MANOVA on bilateral sensorimotor cortex and bilateral SMA activations. Mean coordinates of activations are overlaid on representative (A) horizontal and (B) coronal brain outlines. The right hemisphere is shown on the right. Error bars indicate standard deviation along that axis. In B, y coordinates have been ignored and all foci represented on one slice (at the level of the green dotted line in A), so that they may be more easily compared. Thus, it appears that all six foci are located on the same coronal section, which is not the case (as can be seen in A).

Fig. 4. Results from MANOVA on bilateral visual cortex activations. Mean coordinates of activations are overlaid on representative (A) horizontal and (B) coronal brain outlines. Only the posterior part of the brain is depicted on the horizontal outline. The right hemisphere is shown on the right. Error bars indicate standard deviation along that axis. In A, z coordinates have been ignored and in B, y coordinates have been ignored, so that all foci can be represented on one slice.

Mean locations of activations were also statistically similar between children and adults for all eight foci. Although the difference in the location of the left visual cortex activation may be considered significant using a significance threshold of  $P < 0.05$ , this difference was approximately 4 mm and therefore below the resolution of functional imaging data. Variability in location of activation foci was comparable in the two groups, for all regions examined. These findings suggest that functionally similar regions show similar BOLD responses in both children and adults performing a visuomotor task and that spatial normalization does not significantly distort these patterns of brain activation.

The results of the voxel-by-voxel ANOVA support these findings, particularly for the visual cortex, sensorimotor cortex, and SMA. There were other regions of the brain, however, in which significant differences were found in the time courses of children and adults. For example, preliminary results showed that, in the precuneus (Fig. 5; arrowheads), adults had a negative BOLD response, while children had a positive BOLD response. Although it is possible that some regions of significant activity in this image may have been generated by suboptimal spatial normalization, these results actually support the opposite conclusion.

Suboptimal spatial normalization is likely to result in displacement of functionally similar foci, or large differences in variability between the two groups. Thus, one would expect to find positive BOLD responses for one group and not the other in a particular region, while in a nearby region, the opposite may be true. It is difficult to explain the pattern of time courses in the precuneus through suboptimal spatial normalization. In fact, the presence of negative and positive time courses for the two groups in a single region can be construed as indirect evidence that the difference is not produced by spatial normalization, but is in fact due to actual physiological differences between the two groups.

It is possible that large differences in variability were spuriously generated in regions of the brain not investigated in this study. However, the similarity of anatomical variability between child and adult brains across various sulci, shown by Burgund et al. (2002), suggests that this is unlikely. In addition, variability of activation location seems to be relatively uniform across brain regions. The location variability of higher order association cortex has been found to be similar to that of primary cortex, in language-related regions such as BA 44, BA 47, BA22, and BA 32 (Fox and Pardo, 1991; Xiong et al., 2000), cingulate motor regions (Grafton et al., 1993), anterior cerebellum (Fox et al., 1985b), and extrastriate cortex (Hasnain et al., 1998; Schneider et al., 1994; Watson et al., 1993).

A detailed investigation of all the regions of significant difference between the two groups is beyond the scope of this study. However, the present results provide some evidence to suggest that these differences are not produced by differential normalization of adult and child brains, but may be true physiological differences between the two age groups. In other words, similarity of responses in early cortical processing regions allows us to suggest that differences in higher order cortical regions may indeed be true differences, rather than artifacts of spatial normalization. For instance, some of these regions may be associated with maturational changes, while others may be related to the poorer performance in child subjects (Schlaggar et al., 2002).

One possible criticism of the methodology is that in order to select foci, an anatomical landmark was identified, and the activation on that landmark chosen. However, the fact that the same anatomical landmark was consistently identifiable in a similar location in most subjects, and that there was a functional activation located on or near that landmark, argues for the similarity of adult and child brain functional anatomy in the studied regions.

While we tried to control for task performance by using a relatively simple task and having the children practice before the actual scan, our behavioral results show that we did not entirely succeed. In spite of the discrepancy in task performance, however, we found that adult and child functional neuroimaging data are remarkably similar when transformed to a common space, at least for the visual cortex, sensorimotor cortex, and SMA. In addition, although error trials were not removed from the analysis, average time courses for the child subjects were comparable to those of adult subjects in the regions studied.

#### *Spatial normalization*

Spatial normalization, or transformation into a common stereotactic space, is a powerful tool that allows direct statistical comparison of data sets between different subjects (Fox et al., 1985a). Two commonly used templates for adult neuroimaging studies are the Talairach atlas, based on an elderly woman (Talairach and Tournoux, 1988), and the Montreal Neurologic Institute atlas, based on a group of young adults (Collins et al., 1994).

These atlases have not been entirely validated for use in children (but see Burgund et al., 2002, and Muzik et al., 2000), and in fact, concerns have been raised that children's smaller brain sizes and age-dependent differences in proportional brain region size will affect warping their brain images into standard atlases (Caviness et al., 1996; Gaillard

Fig. 5. Group  $\times$  Time interaction image from voxel-by-voxel ANOVA. The right hemisphere is shown on the right. The color scale corresponds to ANOVA-derived Z scores. Two representative slices are shown, a horizontal section through the sensorimotor cortex (left) and a coronal section through the visual cortex (right). Note the lack of statistical significance in the visual cortex, SMA, and sensorimotor cortex (circles), indicating that time series of voxels are similar for children and adults in these regions. On the left, the arrow points to the right sensorimotor focus showing a difference between children and adults. Arrowheads point to the precuneus.

et al., 2001a; Pfefferbaum et al., 1994). These concerns, along with the lack of validation of the spatial normalization procedure in pediatric brains, may have deterred researchers from performing direct statistical comparisons between groups of children and adults.

In order to exploit the full potential of fMRI as a tool for studying human brain development, it is desirable that a stereotactic approach to the analysis of pediatric neuroimaging data be available. The present findings, and those of Burgund et al. (2002) and Muzik et al. (2000), provide evidence that spatial normalization to an adult-derived template is feasible in children at least 7 years of age. Hopefully, this work will encourage researchers of pediatric populations to perform direct statistical comparisons using a common frame of reference.

The present results might not generalize to children younger than 7 years of age. In a study of children with epilepsy, Chugani and colleagues demonstrated that, when compared to an older group of children (ages 7–14), the brains of younger children (ages 2–6) were associated with greater error after spatial normalization to an adult template, resulting in artifacts in SPM analysis (Muzik et al., 2000). Further studies on younger populations need to be done in order to determine the age range at which transformation to a common template is useful. Alternatively, a target atlas derived from both children and adults may prove more feasible for younger children. Such a strategy of an amalgam atlas has been used in studies of aging (Buckner et al., 2000; Snyder et al., 2000).

#### *Recent developmental neuroimaging studies*

Despite the methodological and statistical challenges associated with performing fMRI in pediatric populations, many researchers are using noninvasive imaging methods to study both normal and abnormal brain development. Several recent studies have used fMRI in children to identify the functional neuroanatomy of working memory, response inhibition, verbal fluency, reading, visual recognition, and imagery (Booth et al., 1999; Bunge et al., 2002; Casey et al., 1995, 1997; Gaillard et al., 2000, 2001b; Holland et al., 2001; Klingberg et al., 2002; Nelson et al., 2000; Thomas et al., 1999). Studies have also analyzed differences in patterns of brain activation between normal children and children with dyslexia (Temple et al., 2001) or attention-deficit hyperactivity disorder (Vaidya et al., 1998). Many of these studies have made conclusions based on the presence or the absence of activations and their extent, rather than direct statistical comparisons.

A few researchers have utilized both spatial normalization to a template brain and direct voxelwise statistical comparison to characterize differences in brain activations between children and adults in tests of lexical processing (Schlaggar et al., 2002) and response suppression (Luna et al., 2001).

One example of the effect of direct voxelwise comparison was demonstrated in a recent study on single word

lexical processing in school-age children and adults (Schlaggar et al., 2002). After transformation of all images to a common stereotactic space, the main effect of time images for each group showed similar patterns of activation. A voxel-by-voxel ANOVA was then performed on all subjects, with Time as a within-subject factor and Group as a between-subject factor. The Group  $\times$  Time interaction image revealed several regions of differential activity between children and adults. These results would not have been found with simple voxelwise addition and subtraction of the main effect of time images from each group. Thus, this study highlights the importance of direct inferential statistical comparison within a common frame of reference.

#### **Conclusion**

A stereotactic approach to the comparison of adult and pediatric neuroimaging data would allow children at various developmental stages to be compared with each other and with adults, thus facilitating the study of cognitive development. Prerequisite to such an approach, we must be satisfied that the BOLD response is not different between children and adults and that the spatial normalization procedure itself is not producing spurious anatomical or functional differences. Previously, we have found few anatomical differences in the brains of children ages 7 and 8 and adults transformed into a common space. In the present research, minimal functional activation differences were found in these same age groups. Although by no means an extensive comparison, these two studies provide preliminary evidence for the validity of using a common stereotactic space for direct statistical comparison of adult and pediatric fMRI data.

#### **Acknowledgments**

We thank Francis Miezin and Jason Nelles for help with experimental design and Rebecca Coalson and Rebecca Dunlap for help with data collection. This research was supported by the McDonnell Center for Higher Brain Function (S.E.P. and B.L.S.) and by NIH Grants NSADA (B.L.S.), NS32979 (S.E.P.), and NS41255 (S.E.P.). B.L.S. is a Scholar of the Child Health Research Center of Excellence in Developmental Biology at Washington University School of Medicine (HD01487). Portions of this work were reported at the Society for Neuroscience 31st Annual Meeting, San Diego, CA (November 2001), and the Cognitive Neuroscience Society 9th Annual Meeting, San Francisco, CA (April 2002).

#### **References**

Beck, J.V., Arnold, K.J., 1977. *Parameter Estimation in Engineering and Science*. Wiley, New York.

- Belliveau, J.W., Kennedy, D.N., McKinstry, R.C., Buchbinder, B.R., Weisskoff, R.M., Cohen, M.S., Vevea, J.M., Brady, T.J., Rosen, B.R., 1991. Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* 254, 716–718.
- Booth, J.R., Macwhinney, B., Thulborn, K.R., Sacco, K., Voyvodic, J., Feldman, H.M., 1999. Functional organization of activation patterns in children: whole brain fMRI imaging during three different cognitive tasks. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 23, 669–682.
- Buckner, R.L., Snyder, A.Z., Sanders, A.L., Raichle, M.E., Morris, J.C., 2000. Functional brain imaging of young, nondemented, and demented older adults. *J. Cogn. Neurosci.* 12, 24–34.
- Bunge, S.A., Dudukovic, N.M., Thomason, M.E., Vaidya, C.J., Gabrieli, J.D., 2002. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. *Neuron* 33, 301–311.
- Burgund, E.D., Kang, H.C., Kelly, J.E., Buckner, R.L., Snyder, A.Z., Petersen, S.E., Schlaggar, B.L., 2002. The feasibility of a common stereotactic space for children and adults in fMRI studies of development. *NeuroImage* 17, 184–200.
- Casey, B.J., Cohen, J.D., Jezzard, P., Turner, R., Noll, D.C., Trainor, R.J., Giedd, J., Kaysen, D., Hertz-Pannier, L., Rapoport, J.L., 1995. Activation of prefrontal cortex in children during a nonspatial working memory task with functional MRI. *NeuroImage* 2, 221–229.
- Casey, B.J., Trainor, R.J., Orendi, J.L., Schubert, A.B., Nystrom, L.E., Giedd, J.N., Castellanos, F.X., Haxby, J.V., Noll, D.C., Cohen, J.D., Forman, S.D., Dahl, R.E., Rapoport, J.L., 1997. A developmental functional MRI study of prefrontal activation during performance of a go-no-go task. *J. Cogn. Neurosci.* 9, 835–847.
- Caviness, V.S., Kennedy, D.N., Richelme, C., Rademacher, J., Filipek, P.A., 1996. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. *Cereb. Cortex* 6, 726–736.
- Cohen, J.D., MacWhinney, B., Flatt, M., Provost, J., 1993. PsyScope: a new graphic interactive environment for designing psychology experiments. *Behav. Res. Methods Instr. Comput.* 25, 257–271.
- Collins, D.L., Neelin, P., Peters, T.M., Evans, A.C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J. Comput. Assist. Tomogr.* 18, 192–205.
- Evans, A.C., Kamber, M., Collins, D.L., MacDonald, D., 1994. An MRI-based probabilistic atlas of neuroanatomy. *Magn. Reson. Scanning Epilepsy (NATO ASI Ser. A, Life Sci.)* 254, 263–274.
- Fox, P.T., Burton, H., Raichle, M.E., 1987. Mapping human somatosensory cortex with positron emission tomography. *J. Neurosurg.* 67, 34–43.
- Fox, P.T., Mintun, M.E., Raichle, M.E., Miezin, F.M., Allman, J.M., Van Essen, D.C., 1986. Mapping human visual cortex with positron emission tomography. *Nature* 323, 806–809.
- Fox, P.T., Pardo, J.V., 1991. Does inter-subject variability in cortical functional organization increase with neural ‘distance’ from the periphery? in: *Exploring Brain Functional Anatomy with Positron Emission Tomography*, Wiley, New York, pp. 125–144.
- Fox, P.T., Perlmutter, J.S., Raichle, M.E., 1985a. A stereotactic method of anatomical localization for positron emission tomography. *J. Comput. Assist. Tomogr.* 9, 141–153.
- Fox, P.T., Raichle, M.E., Thach, W.T., 1985b. Functional mapping of the human cerebellum with positron emission tomography. *Proc. Natl. Acad. Sci. USA* 82, 7462–7466.
- Friston, K., Jezzard, P., Turner, R., 1994. Analysis of functional MRI time-series. *Hum. Brain Mapp.* 1, 153–171.
- Gaillard, W.D., Grandin, C.B., Xu, B., 2001a. Developmental aspects of pediatric fMRI: considerations for image acquisition, analysis, and interpretation. *NeuroImage* 13, 239–249.
- Gaillard, W.D., Hertz-Pannier, L., Mott, S.H., Barnett, A.S., LeBihan, D., Theodore, W.H., 2000. Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology* 54, 180–185.
- Gaillard, W.D., Pugliese, M., Grandin, C.B., Branietcki, S.H., Kondapaneni, P., Hunter, K., Xu, B., Petrella, J.R., Balsamo, L., Basso, G., 2001b. Cortical localization of reading in normal children: an fMRI language study. *Neurology* 57, 47–54.
- Grafton, S.T., Woods, R.P., Mazziotta, J.C., 1993. Within-arm somatotopy in human motor areas determined by positron emission tomography imaging of cerebral blood flow. *Exp. Brain Res.* 95, 172–176.
- Hajnal, J.V., Saeed, N., Soar, E.J., Oatridge, A., Young, I.R., Bydder, G.M., 1995. A registration and interpolation procedure for subvoxel matching of serially acquired MR images. *J. Comput. Assist. Tomogr.* 19, 289–296.
- Hasnain, M.K., Fox, P.T., Woldorff, M.G., 1998. Intersubject variability of functional areas in the human visual cortex. *Hum. Brain Mapp.* 6, 301–315.
- Holland, S.K., Plante, E., Weber Byars, A., Strawsburg, R.H., Schmithorst, V.J., Ball Jr., W.S., 2001. Normal fMRI brain activation patterns in children performing a verb generation task. *NeuroImage* 14, 837–843.
- Josephs, O., Turner, R., Friston, K., 1997. Event-related fMRI. *Hum. Brain Mapp.* 5, 243–248.
- Klingberg, T., Forssberg, H., Westerberg, H., 2002. Increased brain activity in frontal and parietal cortex underlies the development of visuo-spatial working memory capacity during childhood. *J. Cogn. Neurosci.* 14, 1–10.
- Lancaster, J.L., Glass, T.G., Lankipalli, B.R., Downs, H., Mayberg, H., Fox, P.T., 1995. A modality-independent approach to spatial normalization of tomographic images of the human brain. *Hum. Brain Mapp.* 3, 209–223.
- Lee, B.C., Kuppusany, K., Grueneich, R., El Ghazzany, O., Gordon, R.E., Lin, W., Haacke, E.M., 1999. Hemispheric language dominance in children demonstrated by functional magnetic resonance imaging. *J. Child Neurol.* 14, 78–82.
- Luna, B., Thulborn, K.R., Munoz, D.P., Merriam, E.P., Garver, K.E., Minshew, N.J., Keshavan, M.S., Genovese, C.R., Eddy, W.F., Sweeney, J.A., 2001. Maturation of widely distributed brain function subserves cognitive development. *NeuroImage* 13, 786–793.
- Martin, E., Joeri, P., Loenneker, T., Ekatothramis, D., Vitacco, D., Hennig, J., Marcar, V.L., 1999. Visual processing in infants and children studied using functional MRI. *Pediatr. Res.* 46, 135–140.
- Miezin, F.M., Maccotta, L., Ollinger, J.M., Petersen, S.E., Buckner, R.L., 2000. Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage* 11, 735–759.
- Mintun, M.A., Fox, P.T., Raichle, M.E., 1989. A highly accurate method of localizing regions of neuronal activation in the human brain with positron emission tomography. *J. Cereb. Blood Flow Metab.* 9, 96–103.
- Muzik, O., Chugani, D.C., Juhasz, C., Shen, C., Chugani, H.T., 2000. Statistical parametric mapping: assessment of application in children. *NeuroImage* 12, 538–549.
- Nelson, C.A., Monk, C.S., Lin, J., Carver, L.J., Thomas, K.M., Truwit, C.L., 2000. Functional neuroanatomy of spatial working memory in children. *Dev. Psychol.* 36, 109–116.
- Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc. Natl. Acad. Sci.* 87, 9868–9872.
- Ollinger, J.M., Shulman, G.L., Corbetta, M., 2001. Separating processes within a trial in event-related functional MRI I. The method. *NeuroImage* 13, 210–217.
- Pfefferbaum, A., Mathalon, D.H., Sullivan, E.V., Rawles, J.M., Zipursky, R.B., Lim, K.O., 1994. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch. Neurol.* 51, 874–887.
- Picard, N., Strick, P.L., 1996. Motor areas of the medial wall: a review of their location and functional activation. *Cereb. Cortex* 6, 342–353.
- Poldrack, R.A., Pare-Blagoev, E.J., Grant, P.E., 2002. Pediatric functional magnetic resonance imaging: progress and challenges. *Top. Magn. Reson. Imaging* 13, 61–70.
- Ramsey, N.F., Kirkby, B.S., Van Gelderen, P., Berman, K.F., Duyn, J.H., Frank, J.A., Mattay, V.S., Van Horn, J.D., Esposito, G., Moonen, C.T., Weinberger, D.R., 1996. Functional mapping of human sensorimotor cortex with 3D BOLD fMRI correlates highly with H2 15 O PET rCBF. *J. Cereb. Blood Flow Metab.* 16, 755–764.

- Sastre-Janer, F.A., Regis, J., Belin, P., Mangin, J.F., Dormont, D., Masure, M.C., Remy, P., Frouin, V., Samson, Y., 1998. Three-dimensional reconstruction of the human central sulcus reveals a morphological correlate of the hand area. *Cereb. Cortex* 8, 641–647.
- Schlaggar, B.L., Brown, T.T., Lugar, H.M., Visscher, K.M., Miezin, F.M., Petersen, S.E., 2002. Functional neuroanatomical differences between adults and children in the processing of single words. *Science* 296, 1476–1479.
- Schlaug, G., Knorr, U., Seitz, R.J., 1994. Inter-subject variability of cerebral activations in acquiring a motor skill: a study with positron emission tomography. *Exp. Brain Res.* 98, 523–534.
- Schneider, W., Casey, B.J., Noll, D., 1994. Functional MRI mapping of stimulus rate effects across visual processing stages. *Hum Brain Mapp.* 1, 117–133.
- Snyder, A.Z., 1996. Difference image vs. ratio image error function forms in PET-PET realignment, in: Myer, R., Cunningham, V.J., Bailey, D.L., Jones, T. (Eds.), *Quantification of Brain Function Using PET*, Academic Press, San Diego, CA, pp. 131–137.
- Snyder, A.Z., Sanders, A.L., Linenweber, W., Morris, J.C., Buckner, R.L., 2000. Automatic atrophy assessment AAA in young, middle-aged, nondemented and demented older adults. *Cogn. Neurosci. Soc. Abstr.* 7.
- Talairach, J., Tournoux, P., 1988. *Co-Planar Stereotaxic Atlas of the Human Brain*, Thieme Medical Publishers, Inc., New York.
- Temple, E., Poldrack, R.A., Salidis, J., Deutsch, G.K., Tallal, P., Merzenich, M.M., Gabrieli, J.D., 2001. Disrupted neural responses to phonological and orthographic processing in dyslexic children: an fMRI study. *Neuroreport* 12, 299–307.
- Thomas, K.M., King, S.W., Franzen, P.L., Welsh, T.F., Berkowitz, A.L., Noll, D.C., Birmaher, V., Casey, B.J., 1999. A developmental functional MRI study of spatial working memory. *NeuroImage* 10, 327–338.
- Vaidya, C.J., Austin, G., Kirkorian, G., Ridlehuber, H.W., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 1998. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proc. Natl. Acad. Sci. USA* 95, 14494–14499.
- Watson, J.D.G., Myers, R., Frackowiak, R.S.J., Hajnal, J.V., Woods, R.P., Mazziotta, J.C., Shipp, S., Zeki, S., 1993. Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb. Cortex* 3, 79–94.
- Worsley, K.J., Friston, K.J., 1995. Analysis of fMRI time-series revisited—again. *NeuroImage* 2, 173–181.
- Xiong, J., Rao, S., Jerabek, P., Zamarripa, F., Woldorff, M., Lancaster, J., Fox, P.T., 2000. Intersubject variability in cortical activations during a complex language task. *NeuroImage* 12, 326–339.
- Yousry, T.A., Schmid, U.D., Alkadhi, H., Schmidt, D., Peraud, A., Buettner, A., Winkler, P., 1997. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain* 120, 141–157.
- Zarahn, E., Aguirre, G.K., D’Esposito, M., 1997. Empirical analyses of BOLD fMRI statistics: I. Spatially unsmoothed data collected under null-hypothesis conditions. *NeuroImage* 5, 179–197.