Relationships between Brain Activation and Brain Structure in Normally Developing Children

Dynamic changes in brain structure, activation, and cognitive abilities co-occur during development, but little is known about how changes in brain structure relate to changes in cognitive function or brain activity. By using cortical pattern matching techniques to correlate cortical gray matter thickness and functional brain activity over the entire brain surface in 24 typically developing children, we integrated structural and functional magnetic resonance imaging data with cognitive test scores to identify correlates of mature performance during orthographic processing. Fast-naming individuals activated the right fronto-parietal attention network in response to novel fonts more than slow-naming individuals, and increased activation of this network correlated with more mature brain morphology in the same fronto-parietal region. These relationships remained even after effects of age or general cognitive ability were statistically controlled. These results localized cortical regions where mature morphology corresponds to mature patterns of activation, and may suggest a role for experience in mediating brain structure-activation relationships.

Keywords: attention, fMRI, imaging, language, morphometry

Introduction

Structural brain imaging studies have revealed dynamic spatial and temporal patterns of brain development, but how such morphological changes relate to cognitive skills remain largely unexplored. Specifically, the dorsal cortices of the frontal and parietal lobes show dramatic and regionally variable trajectories of change during childhood and adolescence (Sowell, Thompson, Holmes, Jernigan, et al. 1999; Sowell et al. 2001, 2003; Gogtay et al. 2004; Sowell, Thompson, Leonard, et al. 2004; Shaw et al. 2006), with parietal cortices thinning most rapidly between childhood and adolescence (Sowell, Thompson, Holmes, Batth, et al. 1999), and frontal lobes thinning most rapidly between adolescence and young adulthood (Sowell, Thompson, Holmes, Jernigan, et al. 1999). This is important as executive functions attributable to frontal structures (Fuster 2002) continue to develop between adolescence and adulthood. However, considerable variability in cortical structure has been observed cross-sectionally (Sowell et al. 2003), even between individuals of the same age, and the growth trajectory is associated with gray matter thickening in some brain regions and thinning in other regions (Sowell et al. 2003; Sowell, Thompson and Toga 2004; Lu et al. 2007). Such variability challenges efforts to understand the relationship between morphological maturation and cognitive skill maturation.

Significant variability in functional brain activity has also been observed during childhood and adolescence (Turkeltaub et al. 2003; for example). Developmental differences in activation patterns have manifested as a greater extent of activation in children than in adults (Thomas et al. 1999; Gaillard et al. 2000), increase in the degree of hemispheric lateralization with age (Holland et al. 2001), greater intensity of activation in adults than in children (Thomas et al. 1999; Gaillard et al. 2003; Booth et al. 2004), or increased activation with age in key regions related to the task accompanied by decreased activation with age in regions less centrally related to the task (Rivera et al. 2005). It has been speculated that through experience and maturation, there is a shift from more diffuse activation to more focal activation as plasticity declines and efficiency improves (Durston and Casey 2006; Durston et al. 2006), though developmental changes progressing from fewer to greater number of connections have also been proposed and supported (Brown et al. 2005).

It is tempting to speculate that changes in functional activation observed during the childhood and adolescent period of rapid cognitive development are related to changes in brain structure, but little evidence to support this has been reported in the literature. In this study, we used cortical pattern matching techniques to anchor anatomical landmarks across individuals (Sowell, Thompson, Leonard, et al. 2004; Thompson et al. 2004) and integrated structural morphology with corresponding functional activation. Figure 1 depicts the model that guided our study. We first defined “mature” activation by identifying brain regions where activation intensity corresponded with skill level improvement. Then we looked for regions where “mature” activation corresponded with morphological growth trajectories associated with maturation in previous reports (i.e., thinning in dorsal fronto-parietal regions; thickening in perisylvian regions) (Sowell, Thompson, Holmes, Jernigan, et al. 1999; Sowell et al. 2001, 2003; Gogtay et al. 2004; Sowell, Thompson, Leonard, et al. 2004; Shaw et al. 2006). If there are regions of overlap, then morphological maturation is associated with maturation of functional activation. It is important to note that both genetic influences that unfold with age and experience contribute to skill level. We statistically parsed out variance associated with age to illuminate structure-activation relationships independent of age effects. We hypothesized that mature cortical thickness patterns would be associated with mature activation patterns. Specifically, we expected thinning in frontal-parietal regions to be associated with more mature activation patterns during attentional aspects of an orthographic processing functional magnetic resonance imaging (fMRI) task and thickening in perisylvian language regions to be associated with more mature activation patterns on reading aspects of the task.

© The Author 2009. Published by Oxford University Press. All rights reserved. For permissions, please e-mail: journals.permissions@oxfordjournals.org
Brain Activation-Structure Relationships in Children

Task, we chose a cognitive measure whose maturation level was characterized by fluency with orthography: naming speed. The speed with which letters and digits are named becomes faster with age (Wagner et al. 1999), and naming speed in the preschool age range predicts later reading achievement (Wagner et al. 1997; Wolf and Bowers 1999). Naming speed was therefore selected as the operationalized index of cognitive development, and correlations between brain activation and naming speed (i.e., time in seconds) allowed us to identify “mature” patterns of activation with the orthographic processing task. Activation (i.e., increased or decreased) associated with faster naming was defined to be more “mature.”

Materials and Methods

Subjects

Twenty-eight normally developing children without history of neurological, psychiatric, or developmental disorders were recruited from the community near the University of California, Los Angeles, CA. All learned English as their native language. All subjects and their parents gave written assent/consent according to procedures approved by the UCLA Institutional Review Board. Three subjects whose structural or functional scan had inadequate image quality were excluded. One subject was excluded due to excessive movement. Table 1 provides demographic descriptions of the remaining 24 subjects (age ranged from 6 to 15).

Table 1 Demographic description of 24 normally developing subjects and their mean performance on behavioral measures

<table>
<thead>
<tr>
<th>Metric</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range 6–15)</td>
<td>10.54</td>
<td>2.81</td>
</tr>
<tr>
<td>Number of males</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>Handedness quotient*</td>
<td>73.88</td>
<td>23.12</td>
</tr>
<tr>
<td>WISC-4 FSIQ</td>
<td>112.30</td>
<td>15.82</td>
</tr>
<tr>
<td>CTOPP rapid naming standard score*</td>
<td>102.62</td>
<td>12.71</td>
</tr>
<tr>
<td>Ortho word % correct</td>
<td>93.8</td>
<td>7.1</td>
</tr>
<tr>
<td>Ortho false font string % correct</td>
<td>95.3</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*aDexterity quotient from the modified Edinburgh Handedness Inventory (Oldfield 1971).
*bWechsler Intelligence Scale for Children (WISC), 4th ed, prorated FSIQ (Wechsler 2003).
*cComprehensive Test of Phonological Processing (CTOPP; Wagner et al. 1999). WISC and CTOPP scores have a mean of 100 and SD of 15.

Functional Task

Orthographic processing is a skill which develops rapidly during childhood (Sprenger-Charolles et al. 2003) and involves detection of visual features within printed stimuli. The orthographic processing task described by Turkeltaub et al. (2003) required subjects to identify a character in visually presented stimuli of either real words or false font strings (e.g., k, l for the real word condition, and similar nonletter tall characters in the false font string condition) by button press with their right index finger and to indicate absence with their right middle finger (Fig. 2). This task (Turkeltaub et al. 2003) was ideal for our purposes because it activates both brain regions whose maturational trajectory is characterized by gray matter thickening (i.e., primary language cortices in the perisylvian region) as well as regions characterized by thinning (i.e., dorsal fronto-parietal regions) (Sowell, Thompson, Leonard, et al. 2004). The false font string minus word contrast was thought to reflect attentional response to the salience of novel print, as all task demands for the false font string and word conditions were exactly the same except that false font strings were novel, word-like stimuli never seen before. The word minus false font string contrast was thought to reflect implicit reading. Stimuli and task parameters were exactly as described by Turkeltaub et al. (2003) except interstimulus fixation lasted 2.8 s and intercondition rest period lasted 16 s.

Behavioral Tasks

Because our functional activation task was an orthographic processing task, we chose a cognitive measure whose maturation level was characterized by fluency with orthography: naming speed. The speed with which letters and digits are named becomes faster with age (Wagner et al. 1999), and naming speed in the preschool age range predicts later reading achievement (Wagner et al. 1997; Wolf and Bowers 1999). Naming speed was therefore selected as the operationalized index of cognitive development, and correlations between brain activation and naming speed (i.e., time in seconds) allowed us to identify “mature” patterns of activation with the orthographic processing task. Activation (i.e., increased or decreased) associated with faster naming was defined to be more “mature.”

Structural Image Acquisition

High-resolution T1-weighted sagittal volumes were collected from a 1.5 Tesla (T) Siemens Sonata scanner (repetition time [TR], 1900 ms; echo time [TE], 4.38 ms; flip angle, 15°; matrix size, 256 × 256 × 160; field of view [FOV], 256 mm; voxel size, 1 × 1 × 1 mm; acquisition time, 8 min, 8 s). We chose to acquire the structural images on the 1.5T magnet because it yields less susceptibility artifact than the 3T magnet, thus allowing more consistent tissue segmentation throughout the volume. Two to 4 acquisitions were acquired for each subject. Raters blind to subject age and sex evaluated image quality, and data from at least 2 acquisitions were averaged to enhance signal-to-noise ratio. There was no significant relationship between the number of image acquisitions used and age (Pearson’s r = 0.21, P = 0.32).
Functional Image Acquisition

Functional imaging data were obtained from a 3T Siemens Allegra head-only scanner. First, we acquired a high-resolution structural T1-weighted echo-planar image (EPI) volume in the anterior commissure-posterior commissure plane (TR, 5000 ms; TE, 33 ms; matrix size, 128 x 128; FOV, 20 cm; 36 slices; voxel size, 1.6 x 1.6 x 3; 3 mm thick; 1-mm gap) coplanar with the functional scan to allow for spatial registration of each subject’s data into a standard coordinate system. During the orthorhaphic processing task, one functional scan lasting 7 min and 52 s was acquired covering the whole brain volume (116 images; EPI gradient echo sequence; TR, 4000 ms; TE, 25 ms; flip angle, 90°; matrix size, 64 x 64; FOV, 20 cm; 36 slices; voxel size, 3.1 x 3.1 x 3; 3 mm thick; 1 mm gap). The EPI acquisition available on the 3T magnet allows us to collect more image volumes, with better signal-to-noise ratio and shorter scanning time than would be possible on the 1.5T magnet. Thus, functional and structural data were acquired on 2 different magnets, and spatially registered in image processing.

Subjects viewed visual stimuli from magnet-compatible goggles containing 2 miniature television screens with full 512 x 512 resolution (Resonance Technology, Northridge, CA). Stimuli were presented using MacStim 3.2 psychological experimentation software (WhiteAnt Occasional Publishing, West Melbourne, Australia).

Structural Imaging Data Analysis

Preprocessing of high-resolution structural imaging data from the 1.5T scanner were identical to those described previously (Sowell et al. 2002; Sowell, Thompson, Leonard, et al. 2004). Briefly, the MR images were preprocessed with a series of manual and automated procedures executed by analysts blind to subject age and sex: 1) transform brain volumes into a standardized 3D coordinate space (Mazziotta et al. 1995) using a 12 parameter, linear, automated image registration algorithm (Woods et al. 1993); 2) semiautomated tissue segmentation was conducted for each volume data set to classify voxels based on signal intensity as most representative of gray matter, white matter, or cerebral spinal fluid (Shattuck et al. 2001); 3) remove nonbrain tissue (i.e., scalp, orbits) and the cerebellum, and exclude the left hemisphere from the right; i) automatically extract the cortical surface of each hemisphere, which was represented as a high-resolution mesh of 131 072 triangulated elements spanning 65 536 surface points in each hemisphere (MacDonald et al. 1994); 5) trace 35 sulcal and gyral landmarks on the lateral and medial surfaces of each hemisphere using detailed criteria that we have developed (Sowell et al. 2002) for delineating the starting and stopping points for each sulcus using brain surface atlases as references (Ono et al. 1990; Duvernoy et al. 1991) (17 on the lateral surface of each hemisphere: Sylvian fissure, central, precenral, postcentral, superior temporal sulcus (STS) main body, STS ascending branch, STS posterior branch, inferior temporal, superior frontal, inferior frontal, intraparietal, primary intermediate sulcus, secondary intermediate sulcus, transverse occipital, occipito-temporal, and collateral sulci. Twelve on each interhemispheric surface: callosal sulcus, inferior callosal outline, superior rostral sulcus, inferior rostral sulcus, paracentral sulcus, anterior and posterior segments of the cingulate sulcus, outer segment double parallel cingulate sulcus when present, parieto-occipital sulcus, anterior and posterior segments of the calcinar sulcus, and the subparietal sulcus. Six midline landmark curves bordering the longitudinal fissure were delineated to establish hemispheric gyral limits); 6) transform these models from each subject into correspondence with a cortical surface mesh model from each subject; 7) perform high-dimensional continuum mechanical image warping (Thompson et al. 2004). This cortical pattern matching technique, also known as high-dimensional continuum mechanical image warping (Thompson et al. 2001, 2003), allows the creation of average surface models while accounting for cortical variability across subjects. All analyses of the thickness maps were conducted in each subject’s native (unscaled) space.

To map gray matter thickness onto the surface rendering of each child’s brain, the coordinate of each point on the cortical surface for each child (anatomically matched across individuals) was mapped to the same anatomical location in their “thickness” volume, and the average maximum thickness of gray matter within a 15-mm sphere was calculated. In a previous report, we helped to establish the validity of these methods by showing close regional correspondence between maps of cortical thickness created for normally developing children in vivo (Sowell, Thompson, Leonard, et al. 2004) and for the post mortem data of Von Economo (von Economo 1929). In our earlier report (Sowell, Thompson, Leonard, et al. 2004), we also assessed the test-retest reliability of measures of cortical thickness in individuals scanned twice at short time intervals, demonstrating maximum error estimates of 0.15 mm.

Functional Imaging Data Analysis

Preprocessing and statistical analysis of functional imaging data were carried out using FSL (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain [FMRIb]’s Software Library, Oxford University, Oxford, UK; www.fmrib.ox.ac.uk/fsl). We corrected for motion by using MCFLIRT (Jenkinson et al. 2002) and for slice-timing by using Fourier-space time-series phase-shifting. Nonbrain tissues were removed using BET (Smith 2002). Spatial smoothing was applied with a Gaussian kernel of 6 mm full width at half maximum of 6 mm. Mean-intensity normalization of all volumes by the same factor was applied, as well as highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 15 s).

After preprocessing, statistical analyses were performed at the single-subject level by using the general linear model within FSL (FEAT [FMRI Expert Analysis Tool] version 5.63). Each experimental condition was modeled using a boxcar function convolved with a canonical hemodynamic response function. Time-series statistical analysis was carried out using FILM (FMRIb’s Improved Linear Model) with local autocorrelation correction (Woolrich et al. 2001). Volumes for which greater than 2 mm of correction of motion was required were modeled as a covariate of no interest. Results were rendered on Z-statistic images thresholded using clusters determined by Z > 1.7 and a (corrected) cluster significance threshold of P = 0.05 (Worsley et al. 1992). Each subject’s functional data were first registered to corresponding structural volumes using 6-parameter rigid-body transformation, then spatially normalized to the Montreal Neurological Institute-152 template using 12-parameter affine registration via FLIRT (Jenkinson and Smith 2001; Jenkinson et al. 2002) for group analyses.

Mixed-effects group analyses were carried out using FLAME (FMRIb’s Local Analysis of Mixed Effects) (Beckmann et al. 2003; Woolrich et al. 2004). Variances and parameters resulting from single-subject fixed effects analyses were carried into higher-level mixed-effects analysis to allow for inferences to be drawn at the population level. Higher-level statistical maps were thresholded by using clusters determined by Z > 1.7 and a (corrected) cluster significance threshold of P = 0.05.
Coregistering Functional (3T) and Structural (1.5T) Data

Before correlation between activation and gray matter thickness could be conducted, data acquired from 2 different scanners were coregistered into the same space. Structural T1- and T2-weighted images (from 1.5T and 3T scanners, respectively) were first registered into the standardized International Consortium for Brain Mapping’s 305 3D coordinate space (Mazziotta et al. 1995) using a 12 parameter, linear, automated image registration algorithm (Woods et al. 1993) (transformation 1), then registration was further refined by rigid-body transformation of T2-weighted volume into the T1-weighted space (transformation 2). These 2 transformation files were combined by multiplying together transformation matrices and the result was applied to the activation data (the unthresholded t-map for each subject representing the false font string minus word contrast) to bring the functional activation map into correspondence with the high-resolution structural data collected on the 1.5T magnet. Then the high-dimensional continuum mechanical image warping transformation created from the 1.5T T1-weighted structural data was applied to this 3T T2-weighted structural data (which was registered to the functional activation data also collected on the 3T magnet) to bring both functional activation and cortical thickness into anatomical correspondence. An average activation map (using the unthresholded t-map for each individual) for each individual was created using a spatial smoothing kernel of a 15 mm (radius) sphere, identical to the one used for the cortical thickness maps.

Statistical Analyses

Correlations between the 2 contrasts (t-scores representing the magnitude of false font string minus word and word minus false font string) and gray matter thickness were examined by calculating Pearson’s r correlation coefficients on a point-by-point basis for each cortical surface point (approximately 60 000 per hemisphere). Correlations between the activation at each surface point and naming speed for each individual subject were also calculated. Note that the word minus false font string contrast is simply the inverse of the false font string minus word contrast, and thus statistical maps in Figure 5 were only shown for the false font string minus word contrast. To control for multiple comparisons, we conducted permutation analyses (Nichols and Holmes 2004) by randomly permuting activation intensity values and associated correlates (i.e., gray matter thickness or naming speed) in 1000 new analyses. The number of significant correlations (Pearson’s r with P < 0.05) in these 1000 new analyses fell along a normal curve, against which we compared our observed number of significant correlations with original, nonpermutated data. The observed number of significant correlations was deemed to pass correction for multiple comparisons if the probability of it occurring by chance was less than 0.05. Permutation analyses were conducted within 10 regions of interest (ROIs) in each hemisphere: 6 on the lateral surface and 4 on the medial surface of the brain. Coarse ROIs (Fig. 3) were created for each individual from a probabilistic atlas for the frontal, parietal, temporal, and occipital lobes (Evans et al. 1994) with 2 modifications. First, the frontal lobe was divided into dorsal and ventral ROIs by an axial plane passing through the intersection of the inferior frontal sulcus and the precentral sulcus. Second, we created a perisylvian ROI based on our previous longitudinal study of children whose age range overlapped with the age range of subjects in the present study (Sowell, Thompson, Leonard, et al. 2004). This perisylvian ROI corresponded to the only brain region where we observed gray matter thickening with age.

Multiple regression was used to evaluate the relationship between activation and naming speed with age regressed out. The relationship between activation and naming speed independent of general cognitive development was also evaluated with multiple regression with Full Scale Intelligence Quotient (FSIQ) as covariate.

Results

Functional Task Performance

All 24 subjects performed the orthographic processing task (i.e., correctly identifying words or false font strings with tall characters) with at least 78% accuracy and overall significantly better than chance (one-sample t-test compared to chance performance of 50%, t(23) = 38, P < 0.01), and accuracy was equivalent for word and false font string conditions (see Table 1; paired sample t(23) = -1.25, P = 0.22). Response time (RT) to words and false font strings were similar (paired sample t(23) = 0.60, P = 0.56). Both accuracy rate and response time improved with age (Word accuracy, r = 0.50, P = 0.01; False font string accuracy, r = 0.65, P < 0.01; Word RT, r = -0.56, P < 0.01; False font string RT, r = 0.58, P < 0.01). Because the contrast of interest was the difference between false font string and word conditions, whether accuracy and response time differences between false font string and word conditions were related to age was most pertinent for the purposes of this study, and they were not (Word-false font string accuracy and age, r = -0.02, P = 0.94; Word-false font string RT and age, r = -0.17, P = 0.43).

Functional Task Activation

Cortical pattern matching was used to create group average t-maps (uncorrected) representing attentional response to novel print (false font string minus word contrast) as shown in Figure 4. Also shown are axial slices with activation that survived correction for multiple comparisons in the traditional functional image analysis (cluster threshold of P = 0.05 as evaluated with FSL). Activation of the occipital region is highly significant reflecting greater activity to false font strings than real words, as would be expected given that false font strings are more novel in visual form than real words and thus may elicit more activation of processing streams important for distinguishing visual forms. Fronto-parietal activation is also observed, which survived correction for multiple comparisons.

Figure 3. Regions of interest used in the permutation analyses. Lateral regions are color coded as follows: ventral frontal, yellow; dorsal frontal, pink; temporal, dark blue; occipital, green; parietal, light blue; perisylvian, brick red (created from a statistical map published previously; Sowell, Thompson, Leonard, et al. 2004). Medial regions are color coded as follows: dorsal frontal, purple; ventral frontal, olive green; parietal, dark blue; occipital, red; callosal subcortical area (not tested in permutations), white.
on the right but not on the left. These fronto-parietal regions are part of an attentional network that generates top-down influence on the visual cortex (Kastner and Ungerleider 2000), and thus has been posited to underlie orienting of attention to visual tasks (Fan et al. 2005; Raz and Buhle 2006). Significant activation during implicit reading (word minus false contrast) is observed in the left inferior frontal gyrus and survived correction for multiple comparisons in the traditional functional image analysis as seen on horizontal slices in Figure 4b. Activation in left inferior parietal and posterior temporal regions is subthreshold and observed only with uncorrected t-maps on the cortical surface renderings (Fig. 4b). These results are generally consistent with Turkeltaub et al.’s findings using this same orthographic processing task, where both left inferior
Figure 5. Relationships between activation, gray matter thickness, and naming speed. For all surface maps (a, c, d, and e), cortical surface points with statistically significant Pearson’s $r$ correlation coefficients are differentiated from points with nonsignificant values (gray) by color coding, and 3 different levels of statistical significance ($P \leq 0.05$, 0.01, and 0.005) are rendered. Relationship between activation and gray matter thickness. (a) Negative correlations (i.e., red, orange, yellow) indicate that those with thinner cortex activated the fronto-parietal network more in response to novel print. (b) Scatter plots of 3 right parietal surface points (averaged) show that response to novel print (false
frontal and posterior temporal activation were found in adults but activation in only one of these regions passed threshold in children (Turkeltaub et al. 2003).

**Activation and Gray Matter Thickness**

T-statistic maps representing attentional response to novel print for each subject were correlated with gray matter thickness values for each subject at each cortical surface point (anatomically matched across subjects and between activation and thickness maps within subjects). As shown in Figure 5a, greater attentional response to novel print than real words is associated with thinner cortex in bilateral fronto-parietal networks. Permutation testing was conducted within regions of interest to correct for multiple comparisons, and significant negative relationships in the right dorsal frontal and parietal regions were unlikely to be due to chance (Table 2). The normal maturational trajectory of cortex within dorsal parietal and frontal regions is gray matter thinning during the age range that we studied (Sowell et al. 2003; Gogtay et al. 2004; Sowell, Thompson, Leonard, et al. 2004), and the present sample of subjects conforms to this pattern (Fig. 6). Therefore, more “mature” individuals (i.e., subjects with thinner cortex in these regions) activate the fronto-parietal attentional network more than less “mature” individuals (i.e., subjects with thicker cortex in these regions) when processing novel print compared to real words. In contrast, there was no significant positive relationship between activation and gray matter thickness in the perisylvian region (Fig. 5a). Lack of gray matter thickening in the perisylvian region of the present sample of subjects (Fig. 6) may have contributed to decreased ability to detect activation-morphological relationships in this region.

Because attentional network activation in our experiment is based on activation during one condition (false font strings) relative to another (real words), the relative contribution of each condition must be evaluated for interpretation. Scatter plots for activation and thickness values for the average of 3 cortical surface points chosen from right parietal regions where correlations between thickness and activation were significant (from Fig. 5a) are plotted in Figure 5b. These plots show that the significant correlation between thickness and attentional network activation (false font minus word) is driven more by false font strings (false font minus rest, \( r = -0.36 \)) than by real words (word minus rest, \( r = 0.15 \)).

<table>
<thead>
<tr>
<th>Lateral ROI</th>
<th>Response to novel print and gray matter thickness</th>
<th>Response to novel print and naming speed</th>
<th>Response to novel print and naming speed with age regressed</th>
<th>Response to novel print and naming speed with IQ regressed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response to novel print</td>
<td>Response to novel print</td>
<td>Response to novel print</td>
<td>Response to novel print</td>
</tr>
<tr>
<td></td>
<td>and gray matter thickness</td>
<td>and naming speed</td>
<td>and naming speed with age regressed</td>
<td>and naming speed with IQ regressed</td>
</tr>
<tr>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Dorsal frontal</td>
<td>0.0246</td>
<td>0.0022</td>
<td>0.0326</td>
<td>0.0108</td>
</tr>
<tr>
<td>Ventral frontal</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Parietal</td>
<td>ns</td>
<td>0.0091</td>
<td>ns</td>
<td>0.0075</td>
</tr>
<tr>
<td>Occipital</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.0081</td>
</tr>
<tr>
<td>Temporal</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Perisylvian</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.0198</td>
</tr>
</tbody>
</table>

Note: ns = not significant.

**Figure 6.** Correlation between age and gray matter thickness. Cortical surface points with statistically significant Pearson’s \( r \) correlation coefficients are differentiated from points with nonsignificant values (gray) by color coding, and 3 different levels of statistical significance (\( P \leq 0.05, 0.01, \) and \( 0.005 \)) are rendered. Results conform to documented pattern of cortical thinning in the dorsal fronto-parietal region among larger subject groups with more extended age ranges than in the present study; however, the present study sample did not show cortical thickening in the perisylvian region as others have reported (Sowell et al. 2003; Gogtay et al. 2004; Sowell, Thompson, Leonard, et al. 2004).
Activation and Naming Speed

Activation representing attentional response to novel print (false font minus word) was correlated with naming speed to identify the activation pattern associated with more "mature" skill (i.e., faster-naming speed). Resulting statistical maps (Fig. 5c) bear spatial correspondence to the activation-thickness map in fronto-parietal regions (Fig. 5a). Naming speed was measured by time, and larger values represented slower, or worse, performance. Negative relationships between activation and naming speed indicate that those with more "mature" skill (faster) activated the fronto-parietal attentional network more in response to novel print. Similar relationships are also found in bilateral perisylvian and inferior frontal regions, where more "mature" skill presumably corresponds to other functional demands of processing false font strings compared to real words.

Parceling Skill Level from Age and General Cognitive Development

Both activation–thickness (Fig. 5a) and activation–performance (Fig. 5c) maps indicate greater activation of the fronto-parietal network in response to novel print among individuals with more "mature" skills. Because older subjects were faster at naming ($r = -0.71$, $P < 0.001$), it was possible that relationships between activation and performance were spuriously correlated through shared variance with age. Thus, we re-evaluated the relationship between naming speed and activation using age as a covariate. Resulting statistical maps (Fig. 5d) show regions where naming speed predicted activation in response to novel print independent of age effects. Skill in naming letters is accounting for some of the variance in activation of the fronto-parietal network in response to novel print and the shared age variance does not completely account for the observed relationships between activation and performance.

To examine whether the correlation between activation and naming speed is specific to naming skill level rather than a reflection of general cognitive development, we used FSIQ as a covariate in a separate analysis. Resulting statistical maps (Fig. 5e) look remarkably similar to Figure 5c, indicating that general intellectual functioning does not completely mediate the relationship between naming speed and activation in response to novel print.

Discussion

By integrating functional activity, structural morphology, and cognitive skill performance, we were able to identify brain regions where functional activation during orthographic processing was related to cortical thickness. The correlation between activation and naming speed (shown in Fig. 5c) allowed us to determine that greater difference in activation between false font strings and words reflects a more "mature" pattern of activation. This "mature" pattern of activation was associated with thinner cortex in the right fronto-parietal region (Fig. 5a), where cortex thins during childhood and adolescence (Sowell et al. 2003; Gogtay et al. 2004). These data are consistent with the notion that more "mature" cortical thickness patterns (i.e., thinner) are associated with more "mature" activation patterns. This relationship was preserved in the fronto-parietal attention network even after controlling for age or IQ.

One assumption of the present study is that the orthographic processing task used is facilitated by naming skills. The faster children are at naming letters, the easier it should be to decide if a tall letter is in the stimulus. Naming speed is a learned skill but it also correlates with age. Coupling of age and skill level confounds activation due to genetic influences that unfold with age and activation associated with higher skill level. We attempted to dissociate the 2 by using multiple regression to examine effects of skill level while statistically controlling for age effects. Results showed that activation in the fronto-parietal attention network was still associated with naming speed once the effects of age were covaried out. That is, chronological age does not fully explain the relationship between thinning fronto-parietal cortex and faster-naming speed. As both age and experience with print contribute to naming speed, it is tempting to speculate that the relationship between the fronto-parietal attention network and naming speed reflects experience effects. However, the present study design does not allow for such inference because "experience" was neither quantified nor measured. We are not the only group to have parsed out age effects from activation–skill level relationships. Our findings are consistent with Schlaggar and colleagues’ reports of functional activation that varies independently of age and is performance related (Schlaggar et al. 2002; Brown et al. 2005).

In a separate analysis, we controlled for IQ while examining the relationship between activation and skill level. It is possible that individuals with higher intelligence have faster-naming speed and that activation–naming speed relationship found in fronto-parietal regions is driven by effects of intelligence. Activation of the fronto-parietal attention network was associated with naming speed independent of IQ. This finding is important because it suggests that general cognitive ability does not fully explain activation in the fronto-parietal attention network during orthographic processing. Faster-naming individuals activate this fronto-parietal attention network more regardless of effects of general cognitive ability.

The fronto-parietal attention network is involved in both overt and covert orienting of attention to spatial location (Fan et al. 2005; Raz and Buhle 2006). As reviewed by Kastner and Ungerleider (2000), top-down bias from the attention system to visual processing includes enhancement of neural responses to an attended stimulus and increasing stimulus salience. Functional connectivity of the superior parietal lobe and frontal eye fields put them in a position to serve as sources of top-down biasing signals to visual processing streams (Kastner and Ungerleider 2000). The strongest determinant of neural responsiveness of the lateral intraparietal area turns out to be the salience of the stimulus (Colby and Goldberg 1999). The most parsimonious explanation of enhanced activation of this fronto-parietal attention network among individuals with more advanced skills, after controlling for age or general cognitive ability, is that false font strings appear more salient than real words to those with more advanced naming skill. Naming speed can be enhanced by experience, so sensitivity of this parietal–frontal attention network to false font strings may be a specific consequence of experience. In other words, false font strings and real words may be equally novel to slow-naming individuals (i.e., less experience with print, after accounting for their age or IQ) resulting in less difference in activation between the 2 conditions. But among fast-naming individuals (i.e., more experience with print, after controlling for age or IQ), word stimuli were likely quite familiar and only the false font strings were novel and salient, resulting in greater activation of fronto-parietal attention networks to the false font strings relative to real words.
The functional task used here was initially designed to elicit implicit reading (Turkeltaub et al. 2003). We did not observe statistically significant relationships between cortical thickness and implicit reading activation in classical brain language regions. Cortical thickness in these regions has been shown to increase with age into young adulthood, but variability is much higher and effects much smaller than the thinning that occurs in frontal and parietal cortices during this age range (Sowell et al. 2003). Cortical thickening was not observed in these regions in the present sample, perhaps due to limited cross-sectional sample size or a relatively restricted age range. Activation related to the implicit reading aspects of the task may be less robust than activation related to attentional aspects of the task, as suggested by the observation that activation in posterior perisylvian language regions did not occur in frontal and parietal attention areas for words and false font strings relative to rest using the same task. Our study highlights that the difference in activation pattern of children from that of adults reported in other studies may not reflect differences in the targeted cognitive system under study, but may in fact reflect supportive cognitive systems required to complete the task. “Mature” activation patterns for a given task may involve supportive systems as much as the target system, consistent with other developmental fMRI reports (reviewed in Durston and Casey 2006).

The current results are consistent with the notion that the protracted course of functional activation development in the human brain is associated with skill level, at least in frontal-parietal attention networks, and activation corresponds to more “mature” morphology in these regions. From this, we posit that structural brain development may also be related to skill level and not merely to genetic influences that unfold with age. There may be relationships between mature patterns of activation and morphology in other regions of the brain that we lacked sufficient power to detect. The current study is a correlational study and cannot address if structural maturation allows for learning to take place, or if experience leads to morphological maturation. Nevertheless, integrating structural MRI with functional MRI and neurocognitive performance holds tremendous promise in elucidating structure-performance relationships of high-level cognitive functions specific to humans.

**Notes**

We thank Guinevere Eden’s research group for sharing the stimuli used in the orthographic processing task. *Conflict of Interest*: None declared.

Address correspondence to Elizabeth R. Sowell, PhD, UCLA Laboratory of Neuro Imaging, Department of Neurology, 635 Charles Young Drive South, Suite 225, Los Angeles, CA 90095, USA. Email: esowell@ucla.edu.

**References**


Durston S, Casey BJ. 2006. What have we learned about cognitive development from neuroimaging? Neuropsychologia. 44:2149–2157.


