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Cortical thickness of the frontopolar area in typically developing children and adolescents

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The development of the frontopolar cortex (FPC) through late childhood and adolescence was investigated using measures of cortical thickness. T_1-weighted structural MRIs from 35 typically developing participants aged 8–20 years were used to construct 3D models of the brain, from which cortical thickness was measured. There was a significant inverse association between age and cortical thickness, such that cortical thickness decreased as age increased between 8 and 20 years. There was no effect of laterality or gender on cortical thickness.

Keywords: Frontopolar cortex (FPC); Cortical thickness; Development; Laterality; Gender

Introduction

Compared to other brain regions, the frontopolar area of the human brain has been the focus of only a limited number of investigations. Not surprisingly, much less is known about the development of this area, commonly referred to as Brodmann area 10. Recent advances in brain imaging have enabled researchers to describe patterns of brain maturation in typically developing children and adolescents. For instance, it is known that while overall brain volume remains relatively constant past age 5 (Reiss et al., 1996), reduction in gray matter volume between childhood and early adulthood (Gogtay et al., 2004) contributes to a decreasing ratio of cortical gray-to-white matter shown to occur to age 20 (Pfefferbaum et al., 1994). By adolescence, this decreasing ratio is localized to the frontal and parietal lobes (Sowell et al., 1999a, 2002). Post mortem work (Rabinowicz, 1986) has shown a decrease in cortical thickness of the frontal pole between the ages of 6 and 22 years. These findings are consistent with earlier post mortem work that revealed synaptic density to decline in the frontal cortex between ages 2 and 16 (Huttenlocher, 1979), while myelination continues into adulthood (Yakovlev and Lecours, 1967). Thus, empirical data from recent brain imaging and older post-mortem studies suggest that the cortical ribbon of the frontal lobes thins during late childhood and adolescence.

In this study, we identified in vivo developmental changes in the frontal pole, using recently developed computerized methods for measuring cortical thickness. We compared changes in the FPC with those in two control regions: dorsolateral prefrontal cortex (DLPFC; prefrontal cortex immediately superior and lateral to the FPC) and striate cortex (nonprefrontal cortex).

The first prediction was that cortical thickness of the two prefrontal regions (FPC and DLPFC) would decrease across late childhood and adolescence, while thickness of the striate cortex would not be significantly associated with age. The second prediction, based on evidence of right greater than left hemisphere gray matter volume (Reiss et al., 1996), was that cortical thickness would be greater in the right hemisphere. The third prediction was that, because gray matter volume is ~10% greater in males compared with females (Giedd et al., 1999; Reiss et al., 1996), males would have thicker cortical measurements.

Materials and methods

Participants

Thirty-five typically developing individuals (8–20 years; mean age, 13.3 years; 18 males and 17 females) from the control group

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of the Spina Bifida Project (The Hospital for Sick Children, Toronto and The University of Texas, Houston) were included (approved by the Hospital for Sick Children Research Ethics Committee). Children were recruited through hospital and newspaper advertisements, or were siblings of children enrolled in another hospital-based study. Participants also had no neural tube defect, genetic syndromal disorder, neurological disorder, severe psychiatric disorder (autism, psychosis, oppositional-defiant disorder), uncontrolled seizures, or uncorrected sensory disorder. Information was derived from DSM-IV questionnaires completed by the parents (SNAP-IV; Swanson, 1992), including DSM-IV checklist for autism and pervasive developmental disorders. Medical history pertaining to pregnancy, labor and delivery, and general health was obtained verbally from each child's mother, and from medical chart review. Participants were required to have been born at full term (37–41 weeks gestation), to have Average for Gestational Age birth weights, and to have APGAR scores >6 at 5 min. Participant IQ was within approximately two standard deviations of the population mean of 100 (range 84–116), and each child spoke English as a first language. Following appropriate suitability screening, each participant had a structural 3D MRI scan performed, which was read as normal by an experienced pediatric neuroradiologist.

Imaging protocol

MR imaging was performed at either the Toronto or Houston test site. MR images were acquired with a GE-LX 1.5-T scanner (The Hospital for Sick Children, Toronto) or a GE Horizon 1.5-T scanner (The University of Texas, Houston). At both sites, a standard image acquisition protocol was followed: T_1-weighted 3D spoiled gradient echo sequences were obtained in the coronal plane with flip angle = 25°, TE = 4 ms, TR = 18 ms, field of view = 24 × 24 cm, matrix size = 256 × 192 (zero filled to 256 × 256), slice thickness = 1.5 mm, 15.63 kHz receiver band width, and 124 contiguous slices. The start and end two slices were removed prior to 3D Fourier transformation of the data to eliminate aliasing in the second phase encoding direction.

Cortical reconstruction and calculation of thickness

MR images were processed and average measures of cortical thickness obtained as follows: (1) FreeSurfer (Fischl and Dale, 2000) was used to read MR data, and reconstruct a 3D model of the cortex; (2) each 3D FreeSurfer model was linked to its original MR image, read in AFNI (Analysis of Functional NeuroImages; Cox and Hyde, 1997), using SUMA (Surface Mapping with AFNI; Cox and Hyde, 1997); (3) each original image was transformed to standard space (Talairach and Tournoux, 1988) in AFNI; (4) labels including the left hemisphere FPC and the right hemisphere FPC were applied on each image in standard space, and transferred to the 3D FreeSurfer model via SUMA; (5) labels for the two control regions of interest (frontal lobe control region: DLPFC; non-frontal lobe control region: striate cortex) were similarly applied on each image in standard space, and transferred to the 3D FreeSurfer model via SUMA; (6) average thickness was calculated from the labeled voxels of each region of interest using Matlab (v6.5, The Mathworks, Natick VA). FreeSurfer, AFNI, and SUMA were all run on a Linux platform. Cortical reconstruction using FreeSurfer involved a series of both programmed and manual (see following paragraph) processes that required, on average, 12–15 h per brain for completion. Transformation of the reconstructed images to standard space and labeling of regions of interest using AFNI functions also involved both programmed and manual processes, and could be completed within an hour.

MR data for each participant was read, and a 3D model of the cortex constructed, using FreeSurfer (Fischl and Dale, 2000). As part of the FreeSurfer reconstruction process, the following automated serial manipulations were carried out on each image: (1) all non-brain structures were removed, based on a combination of watershed algorithms and deformable surface models; (2) white matter was isolated (using intensity and geometric data), filled, and tessellated; (3) topological errors were fixed and the surface resmoothed; and (4) cortical reconstruction proceeded outwards from the gray/white surface to the gray/CSF surface (Fig. 1). Prior to the automated correction of topological errors (step 3), necessary surface edits (filling of lateral ventricles and area of the basal nuclei, as well as removal of the fornix and optic nerve) were made manually, guided slice-by-slice by the FreeSurfer Tutorial, to allow white matter to be inflated to a smooth, spherical form.

At the completion of the reconstruction process, a data file existed for each hemisphere, containing localization information and a submillimeter thickness measure of the distance from the gray/white surface to the pial surface for each constituent voxel. The standard error associated with FreeSurfer's measures of cortical thickness is cited in the literature as being ~0.1–0.25 mm (Fischl and Dale, 2000). Tests of FreeSurfer's between-subject and between-protocol reliability and validity have been published (Fischl and Dale, 2000).

Each subject's 3D FreeSurfer surface model was then linked to his or her original MR image, read in AFNI (Cox and Hyde, 1997), using SUMA (Cox and Hyde, 1997). All brain images were transformed linearly to standard space (Talairach and Tournoux, 1988) in AFNI, and labels for the regions of interest were created. The three regions of interest were the FPC (primary area of interest; referred to as Brodmann area 10), the DLPFC

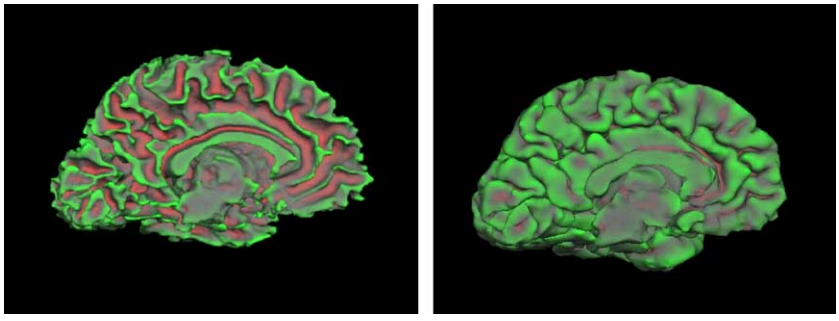

Fig. 1. FreeSurfer reconstruction of the gray/white surface (left); FreeSurfer reconstruction of the pial surface (right).

(frontal lobe control region; located superior and lateral to the FPC, and contained within Brodmann area 46 and the lateral aspect of Brodmann area 9), and the striate cortex (nonfrontal lobe control region; located in the occipital lobe within Brodmann area 17). A left hemisphere label for each of the three regions was traced, slice-by-slice, in the axial plane of one subject's transformed image, based on color-coded Brodmann area masks derived from the Talairach Atlas and supplied in the AFNI software. Each left hemisphere label was then flipped to produce a mirror-image right hemisphere label (using AFNI functions), and the right and left hemisphere labels (in standard space) for each of the three regions of interest were then transferred to every other participant's standard-space image. Because our work was not of an architectonic nature, it is acknowledged that use of Brodmann area masks for the creation of region of interest labels provided only a very general guide for segmenting FPC, DLPFC, and striate cortex. Lack of precision was balanced, however, by the number of measures of cortical thickness taken from coordinate points within each region of interest. Labels of the FPC and the DLPFC contained approximately 3000–5000 voxels (and associated thickness measures) from which average thickness was calculated, while labels of the striate cortex contained ~1000–3000 voxels.

The labels were subsequently opened up on each participant's original image (untransformed, AFNI image) and linked to the corresponding FreeSurfer model (Fig. 2) using SUMA. Those voxels labeled on the FreeSurfer model were isolated from the FreeSurfer thickness data file, and measures of cortical thickness associated with the labeled voxels were averaged using Matlab (v6.5, The Mathworks, Natick VA).

Statistical analyses

Mean cortical thickness and rate of change in thickness were calculated for each of the three regions of interest (FPC, DLPFC, and striate cortex), and correlated with age, sex, and hemisphere to test for significant associations.

Analysis of variance (ANOVA) using a general linear model was performed using SPSS 11.0 (Chicago, IL) for Windows. Between-group comparisons of regression lines were made with one of the Research Support tools of the Chinese University of Hong Kong (StatTools, 2003). Mean cortical thickness, for both

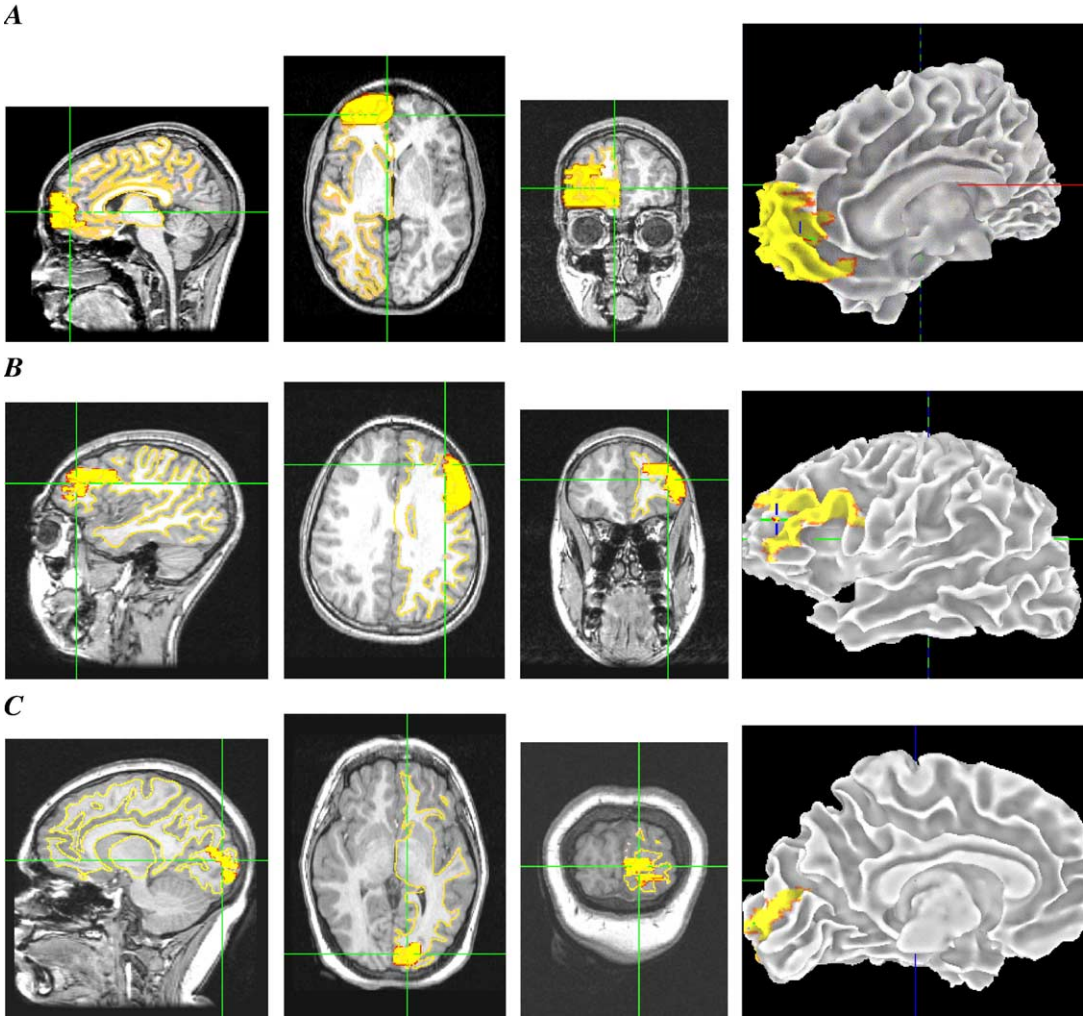

Fig. 2. Labels of (A) the frontopolar cortex (Brodmann area 10), (B) the dorsolateral prefrontal cortex (Brodmann area 46 and the lateral aspect of Brodmann area 9), and (C) the striate cortex (Brodmann area 17) displayed in the sagittal, axial, and coronal views in AFNI, and on the subject's corresponding 3D FreeSurfer model via SUMA.

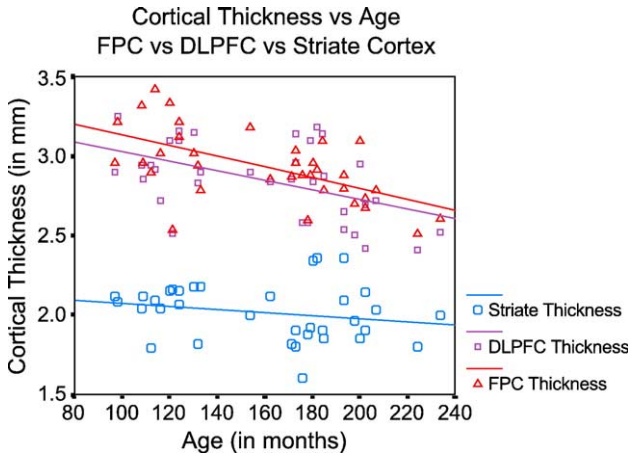

Fig. 3. Plot of cortical thickness of the FPC, the DLPFC, and the striate cortex across the studied age range. Both FPC and DLPFC thickness were significantly associated with age (FPC: $r = -0.591$, $P < 0.0005$; DLPFC: $r = -0.495$, $P < 0.005$). Striate cortical thickness was not significantly associated with age. Difference in mean cortical thickness and rate of change in thickness were not significant between the FPC and the DLPFC, but the FPC was significantly thicker than the striate cortex ($P < 0.0001$).

boys and girls combined, as well as boys only and girls only, was calculated for both hemispheres of each of the three labels (FPC, DLPFC, and striate cortex). Change in cortical thickness across the studied age range for each of the three areas was assessed by measurement of the slope of linear regression lines (slope for boys and girls combined, as well as boys only and girls only was considered). Age distribution of the participants was such that no individual was between the ages of 134 and 155 months (11.2–12.9 years). In order to satisfy concerns that data from this age gap might not be consistent with the trend of our findings, and to ensure the appropriateness of considering data from the entire group as a whole ($N = 35$; 8.1–19.5 years) rather than two subgroups ($N = 14$ for 8.1–11.1 years; $N = 21$ for 12.8–19.5 years), slope of linear regression lines reflecting change in cortical thickness for the younger group and older group was compared for each of the three regions of interest. Pearson correlations were used to determine the association between cortical thickness and age, while one-way ANOVA was used to test the association between cortical thickness and sex.

Results

Cortical thickness: association with age, laterality, and gender

Mean cortical thickness of each of the three regions of interest was calculated for males and females combined (18 males and 17 females; average age 13.3 years). There was no significant difference between mean cortical thickness of the FPC (2.93 ± 0.22 mm) and the DLPFC (2.85 ± 0.24 mm), although mean thickness of the FPC was significantly greater than that of the striate cortex (2.02 ± 0.17 mm; difference in mean cortical thickness = 0.92 mm, $P < 0.0001$). Further, a significant inverse association between age and cortical thickness of the frontopolar region ($r = -0.591$, $P < 0.0005$), and age and cortical thickness of the dorsolateral prefrontal region ($r = -0.495$, $P < 0.005$) existed, but the association between age and thickness of the striate cortex was not significant. Rate of change in cortical thickness (slope of the linear regression line) across the studied developmental time frame did not differ significantly between the two frontal regions, the FPC and the DLPFC (difference between FPC slope and DLPFC slope = 0.0004 mm/month, $P = 0.7664$). Change in cortical thickness across the investigated age range (97–234 months or 8.1–19.5 years) is graphed for the FPC, the DLPFC, and the striate cortex in Fig. 3.

As none of our participants was aged 11.2–12.7 years, the likelihood that data for individuals within this age group would fall within the pattern of our results was tested: slope of change in cortical thickness for the younger group (8.1–11.1 years) was compared with slope for the older group (12.8–19.5 years) for each of the three regions of interest. There was no significant difference between slope for the younger group versus the older group in the FPC (difference between slopes = −0.0005, $P = 0.9240$), the DLPFC (difference = −0.0058, $P = 0.2991$), or the striate cortex (difference = −0.0002, $P = 0.9623$). Therefore, investigation of association between thickness, laterality and gender was conducted using data from the entire group ($N = 35$; 8.1–19.5 years).

Cortical thickness measures of the FPC and the DLPFC were plotted against age in order to determine whether a plateau in decline of thickness existed at the upper end of the age boundary (Fig. 4). The first-order exponential model (describing a decline in thickness with age) did not reveal a plateau in the decrease in

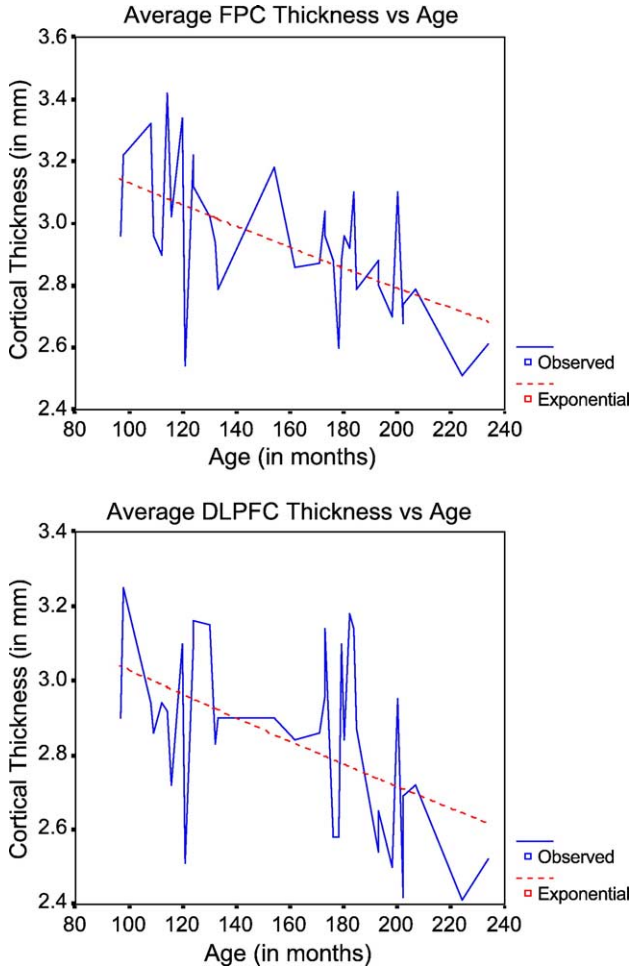

Fig. 4. Exponential model of change in thickness of the FPC (top) and the DLPFC (bottom) with age.

Table 1
Measures of mean cortical thickness for the left and right hemispheres of the FPC, the DLPFC, and the striate cortex

Left vs. right hemisphere measures of cortical thickness		
Region of interest	Mean cortical thickness (mm)	Standard deviation (mm)
Left FPC	2.92	0.21
Right FPC	2.94	0.25
Left DLPFC	2.86	0.23
Right DLPFC	2.84	0.27
Left striate cortex	2.00	0.18
Right striate cortex	2.03	0.19

cortical thickness observed with age. Thus, it seems that between 97 and 234 months (8.1–19.5 years), the decline in cortical thickness of the FPC and the DLPFC is linear in nature.

In order to test for an effect of laterality on cortical thickness, mean cortical thickness of the left and right hemispheres was calculated separately for each of the three regions of interest (Table 1). No significant difference between left and right hemisphere mean cortical thickness was found in any of the three regions (FPC difference between left and right hemisphere mean thickness = 0.02 mm, $P = 0.6359$; DLPFC difference = 0.02 mm, $P = 0.7269$; striate cortex difference in means = 0.03 mm, $P = 0.4821$). The association between age and cortical thickness of the frontopolar area in both hemispheres was significant (left hemisphere: $r = -0.549$, $P < 0.005$; right hemisphere: $r = -0.591$, $P < 0.0005$). Age was also significantly correlated with cortical thickness in both hemispheres of the dorsolateral prefrontal region (left hemisphere: $r = -0.416$, $P < 0.05$; right hemisphere: $r = -0.508$, $P < 0.005$). No association between age and cortical thickness in either hemisphere of the striate region was significant at the $P < 0.05$ level.

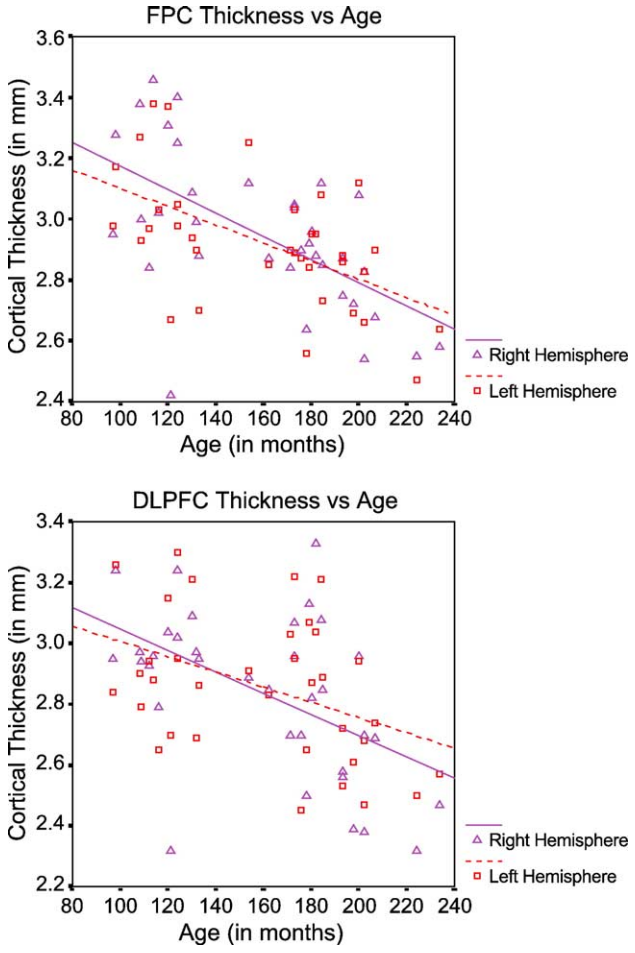

Fig. 5. Plot of right and left hemisphere cortical thickness across the studied age range. Top: FPC (left hemisphere association between age and thickness: $r = -0.549$, $P < 0.005$; right hemisphere: $r = -0.591$, $P < 0.0005$). Bottom: DLPFC (left hemisphere association between age and thickness: $r = -0.416$, $P < 0.05$; right hemisphere: $r = -0.508$, $P < 0.005$).

Comparison of the rate of change in cortical thickness (slope of the linear regression line) in the left versus right hemisphere for both the frontopolar region and the dorsolateral prefrontal region failed to reveal any significant difference (FPC difference in right vs. left hemisphere change in thickness = 0.0008 mm/month, $P = 0.4864$; DLPFC difference = 0.0010 mm/month, $P = 0.4816$) (Fig. 5).

Mean cortical thickness in each of the three labeled regions (FPC, DLPFC, and striate cortex) was calculated for males ($N = 18$; mean age = 13.7 years) and females ($N = 17$; mean age = 12.9 years) separately (Table 2). One-way analysis of variance revealed no significant difference between mean cortical thickness observed in males and females in the FPC ($F = 3.321$, $P = 0.077$), the DLPFC ($F = 2.075$, $P = 0.159$), or the striate cortex ($F = 0.235$, $P = 0.631$). In the left hemisphere FPC, however, difference in mean cortical thickness between females and males (females > males) approached significance ($F = 3.797$, $P = 0.060$). Adjusting for age (mean age of the females was 0.8 years younger than mean age of the males), did not change this ($P = 0.07$).

Rate of change in cortical thickness across the studied age range was not different between females and males in the left FPC (difference in slopes = 0.0000, $P = 0.980$) or right FPC (difference in slopes = 0.0000, $P = 0.997$) (Fig. 6).

Discussion

The results of this study show that, across a sample of typically developing children and adolescents, cortical thickness is inversely associated with age in two regions of the prefrontal cortex: the frontopolar region and dorsolateral prefrontal region. This decrease is not significantly different between the two regions and does not

Table 2
Measures of mean cortical thickness of the FPC, the DLPFC, and the striate cortex for males and females

Males vs. females measures of cortical thickness			
Region of interest		Mean cortical thickness (mm)	Standard deviation (mm)
Left FPC	Males	2.86	0.19
	Females	2.99	0.22
Right FPC	Males	2.88	0.25
	Females	3.01	0.25
Left DLPFC	Males	2.80	0.23
	Females	2.92	0.23
Right DLPFC	Males	2.79	0.30
	Females	2.89	0.23
Left striate cortex	Males	2.00	0.21
	Females	2.01	0.14
Right striate cortex	Males	2.01	0.20
	Females	2.06	0.18

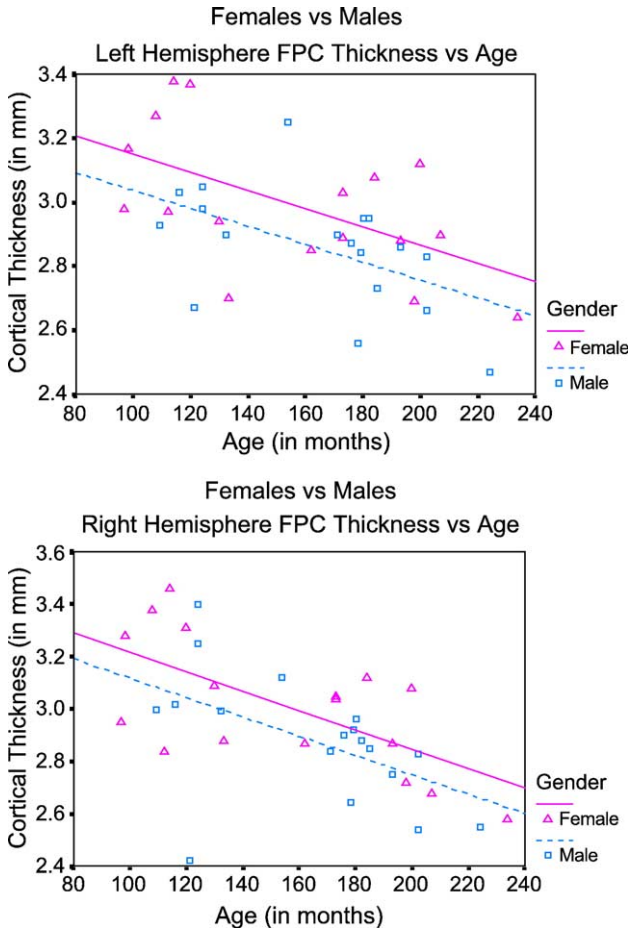

Fig. 6. Plots comparing FPC thickness of males and females across the studied age range. No significant differences existed between males and females for average mean thickness or rate of change in thickness.

appear to be influenced by laterality or gender. No association between age and striate cortical thickness was found.

The significant inverse association between age and FPC thickness is consistent with Rabinowicz's post mortem work (1986) and parallels volumetric studies that show frontal gray matter to decrease during adolescence (Gogtay et al., 2004; Sowell et al., 1999a, 2002). Speculation that regressive activity in gray matter and progressive white matter changes drive this developmental pattern is based on evidence of decreasing synaptic density in the human frontal cortex between 2 and 16 years (Huttenlocher, 1979) and continued myelination into adulthood (Yakovlev and Lecours, 1967). Work by Sowell et al. (2001) demonstrates that, in fact, significant gray matter loss occurs in spatial and temporal conjunction with white matter gain. Possible functional implications of this finding are interesting. By eliminating inefficient or unnecessary dendritic connections in the cortical ribbon, more effective, accurate synaptic transmission would be possible. In white matter, increased myelination would improve impulse conduction time, speeding up transmission of signals to and from destination sites in the brain. It is necessary, however, to reiterate that our findings are only able to show that the pattern of developmental change in thickness is consistent with volumetric patterns. Future research relating gray and white matter volumetric changes to changes in cortical thickness is necessary for a more thorough understanding of developmental changes in the frontal lobes.

Laterality of cortical thickness was not significant in any of the three regions of interest (FPC, DLPFC, and striate cortex), for each of which there was no significant difference between right and left hemisphere mean cortical thickness or rate of change in thickness. This is in contrast to Reiss et al.'s (1996) finding of right greater than left cortical gray matter volume in participants over a similar age range. The discrepancy may relate to procedural differences: while Reiss et al. (1996) studied the overall volume of cortical gray matter in each of the hemispheres, we considered only three specific regions (FPC, DLPFC, and striate cortex). Further, hemispheric gray matter volume is theoretically dependent, to a degree, on white matter radius, as gray matter encircles white. It is possible that Reiss et al.'s (1996) finding of an effect of laterality on gray matter volume could be related to hemispheric white matter differences rather than to hemispheric differences in cortical thickness.

In our study, gender did not produce a significant difference between males and females in mean cortical thickness or rate of change in thickness in FPC, DLPFC, or striate cortex. These data are not in agreement with reports of sex differences in frontal lobe volume (Sowell et al., 2002), and specifically, with reports of greater gray matter volume in males than females (Giedd et al., 1999; Reiss et al., 1996) during childhood and adolescence. However, while the volumetric studies evaluated cortical gray matter of the entire frontal lobe, we considered only two precise frontal regions. Further, our work assessed thickness, rather than volume, of the cortical ribbon. It is also necessary to point out that interpretation of our results is limited by a number of factors. First, separating males from females reduced sample size from 35 to 18 and 17, respectively. As well, we did not account for a number of issues that might influence differences in cortical thickness, such as handedness, academic level, and environmental experience. Thus, an absence of gender-associated differences could be related to low power, and remains to be investigated in a large sample.

Our results showed that decrease in FPC (and DLPFC) thickness is linear between ages 8 and 20. In a study in which gray matter density across the life span was plotted, Sowell et al. (2003) found a steep decline in density across the first half of a 0–90-year scale, followed by a plateau in density measures across the second half, in the superior and anterior regions of the frontal lobes. It appears, then, that late childhood and adolescence is a developmental period in which dramatic changes in the prefrontal cortex take place. If developmental regressive activity in gray matter lends to more effective, accurate synaptic transmission, then our data implies that function mediated by the FPC and the DLPFC should be enhanced during this age frame. Interestingly, it has been suggested (Colby and Kohlberg, 1987; Fuster, 1989; Sowell et al., 1999b) that late childhood and adolescence brings improvements in such frontal lobe behaviors as response inhibition, emotional regulation, planning, organization, and moral reasoning.

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