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NeuroImage 26 (2005) 1164 – 1173

Diffusion tensor imaging of neurodevelopment in children and young adults

Lindsay Snook,[a] Lori-Anne Paulson,[a] Dawne Roy,[b] Linda Phillips,[b] and Christian Beaulieu[a,*]

[a]*Department of Biomedical Engineering, Faculty of Medicine and Dentistry, 1098 Research Transition Facility, University of Alberta, Edmonton, AB, Canada T6G 2V2*
[b]*Centre for Research on Literacy, University of Alberta, Edmonton, Alberta, Canada T6G 2G5*

Received 24 November 2004; revised 7 March 2005; accepted 16 March 2005
Available online 28 April 2005

Diffusion tensor magnetic resonance imaging (DTI) was used to study regional changes in the brain's development from childhood (8–12 years, mean 11.1 ± 1.3, *N* = 32) to young adulthood (21–27 years, mean 24.4 ± 1.8, *N* = 28). Mean diffusivity (Trace/3 apparent diffusion coefficient, ADC) and fractional anisotropy (FA) were measured in 30 regions of interest (ROIs) in 13 distinct brain structures. Correlational analysis was performed to detect changes within 8–12 years and within 21–27 years, and group analysis to compare childhood diffusion properties with young adult values. Increases of fractional anisotropy were seen in the genu of the corpus callosum, splenium of the corpus callosum, corona radiata, putamen, and head of the caudate nucleus within 8–12 years, and also between childhood and young adulthood. Reductions in Trace/3 ADC were observed in 9 of 13 structures within 8–12 years and into young adulthood as well. DTI demonstrates more widespread changes in the brain's microstructure with maturation than previous reports using conventional T1-weighted MRI scans. These findings suggest a continuation of the brain's microstructural development through adolescence.

Keywords: Diffusion tensor imaging; Neurodevelopment; Children

Introduction

Magnetic resonance imaging (MRI) has opened the door to localizing maturational changes in the brain (Paus et al., 2001). Postmortem studies, although quite enlightening, are often limited in the numbers of young subjects who are free of complicating diseases, making it difficult to study the normal aging brain (Sowell et al., 2004). T1- and T2-weighted MR imaging studies have shown differences in overall brain volumes with age and gender (Courchesne et al., 2000; Giedd et al., 1999; Sowell et al., 2002). In order to look at more specific tissues rather than just global volume differences, three-dimensional T1-weighted scans have been post processed to look at regional growth rates and tissue density. One longitudinal study found a rostro-caudal wave of growth in the corpus callosum of young children (Thompson et al., 2000). Using voxel-based morphometry, age-related "white matter density" increases have been reported in the internal capsule and the left arcuate fasciculus over 4–17 years of age (Paus et al., 1999). The T1-weighted imaging studies tend to find changes in a limited number of brain regions, and the relationship between the signal intensity on the T1-weighted images and the underlying microstructure is unclear. Diffusion tensor imaging (DTI) of water mobility in tissue may provide a more sensitive measure of the changes in the brain's microstructure with maturation (Le Bihan, 2003).

DTI is sensitive to the Brownian motion of water as it diffuses in the brain. Diffusion is said to be isotropic when it occurs equally in all directions (e.g., when there are no barriers). However, when there is a barrier to impede the motion of the water, such as membranes in a white matter tract, the diffusion is no longer equal in all directions and it is said to be anisotropic (Chenevert et al., 1990; Moseley et al., 1990). The standard tissue diffusion parameters derived from DTI are the average apparent diffusion coefficient (Trace/3 ADC) and fractional anisotropy (FA) (Basser, 1995). Trace/3 ADC is a rotationally invariant measure of the magnitude of diffusion and it is fairly homogenous throughout the brain, with the exception of neonates (Miller et al., 2003), when diffusion-weighted images are acquired at lower diffusion sensitivity factors (i.e., *b*-values up to ~1000 s/mm^2). FA is a measure of the directionality of diffusion with values ranging from 0 (isotropic diffusion) to 1 (highly anisotropic diffusion) and has far greater variability throughout the brain than Trace/3 ADC. Although the interpretation of water diffusion parameters, particularly anisotropy, is not straightforward (Beaulieu, 2002), higher FA values could indicate an increase in fiber bundle density and/or increased myelination with development. The eigenvalues of the diffusion tensor, which

* Corresponding author. Fax: +1 780 492 8259.
E-mail address: christian.beaulieu@ualberta.ca (C. Beaulieu).
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2005.03.016

yield the apparent diffusion coefficients either parallel (λ_1) or perpendicular (λ_2, λ_3) to the white matter tracts, are not often reported but can yield insight into the microstructural changes of the tissue.

DTI has been applied to better understand neurodevelopment in several studies from neonates up to the 8th decade of life (Moseley, 2002; Neil et al., 2002). In adult studies (ages 20 years and above), general maturational trends of increasing Trace/3 ADC and decreasing FA were found (Abe et al., 2002; Bhagat and Beaulieu, 2004; Pfefferbaum et al., 2000). Studies of neonates and children have found opposite trends of decreasing mean diffusivity and increasing anisotropy with age, with the exception of the cortex in preterm infants which shows decreases in anisotropy (McKinstry et al., 2002). More specifically, these increases of FA have been observed in the corpus callosum, internal capsule, caudate head, lentiform nucleus, and thalamus over 1 day to 11 years (Mukherjee et al., 2001), the internal capsule, corticospinal tract, left arcuate fasciculus, and right inferior longitudinal fasciculus over 5–18 years (Schmithorst et al., 2002), and the pons, crus, centrum semiovale, and subcortical white matter over 1 day to 16 years (Schneider et al., 2004). The first and third studies demonstrated that most of the diffusion changes occur within the first 4 years of life. These analyses have been performed with a limited number of ROIs (between 7 and 11) and with thicker slices (5 mm for the first two and 4 mm for the last), and in addition they did not investigate the transition into young adulthood. A separate study investigated this transition period and demonstrated that anisotropy increased from childhood (8–12 years) to adulthood (20–31 years) in the frontal white matter; however, no other brain regions were investigated (Klingberg et al., 1999). No comprehensive DTI studies have examined the potential brain changes occurring between late childhood and young adulthood although it is known that the brain experiences a protracted progression of myelination and axonal growth during adolescence and young adulthood based on histological autopsy studies (Yakovlev and Lecours, 1967) as well as linear increases of total white matter volume on longitudinal T1-weighted in vivo MRI scans (Giedd et al., 1999).

The purpose of this study is to determine what regions of the brain are continuing to develop through late childhood (8–12 years, $N = 32$) and into young adulthood (21–27 years, $N = 28$) using diffusion tensor imaging. FA and Trace/3 ADC were measured in a large number of brain regions to assess microstructural changes associated with brain maturation. Two types of analyses were performed: (i) linear regression within the 8- to 12-year-old children and also within the 21- to 27-year-old young adults; and (ii) group comparisons between the children and young adults. We also report apparent diffusion coefficients parallel and perpendicular to the fiber bundles (i.e., eigenvalues of the diffusion tensor) in the children to interpret any observed changes of diffusion anisotropy with maturation.

Methods

Subjects

Two groups of healthy volunteers were used in this study, namely, 32 children aged 11.1 ± 1.3 (range 8–12 years, 18 female, 14 male, 30 right handed, 2 left handed) and 28 young adults aged 24.4 ± 1.8 (range 21–27 years, 14 female, 14 male, 25 right handed, 3 left handed). All subjects gave informed consent, and parent/guardian consent was given for all volunteers under 18 years of age. Volunteers had no history of psychiatric disease or neurological injury.

Image acquisition

Subjects were scanned with a 1.5-T Siemens Sonata MRI scanner for approximately 26 min for anatomical and DTI imaging. The DTI data were acquired using a dual spin-echo, single shot echo-planar imaging sequence with 3 mm slice thickness, no inter-slice gap (interleaved acquisition), TR = 6400 ms, TE = 88 ms, field-of-view 220 × 220 mm^2, 6 non-collinear diffusion-sensitizing gradient directions with diffusion sensitivity $b = 1000$ s/mm^2, 8 averages, and a matrix of 96 × 128 zero filled to 256 × 256 for a resulting voxel size of 0.85 × 0.85 × 3.0 mm^3. Total DTI acquisition time was 6:06 min with 40 contiguous axial slices for full brain coverage. Slices were positioned along the anterior commissure-posterior commissure line. The mean SNR of brain parenchyma on the non-diffusion-weighted images was 75 ± 6 for the children and 71 ± 6 for the young adults. Representative FA maps of the children and young adults are shown in Fig. 1.

Region-of-interest data collection

Trace/3 ADC and FA values were collected from 30 regions of interest (ROIs), in 13 distinct brain regions, which can be divided into four tissue type categories. (1) Major white matter: genu of corpus callosum, splenium of corpus callosum, anterior limb of the internal capsule, posterior limb of the internal capsule, external capsule, corona radiata, and centrum semiovale; (2) subcortical white matter in gyri: a sample of 5 gyri including the right superior frontal gyrus, right supra marginal gyrus, right middle occipital gyrus, left superior temporal gyrus, and the left postcentral gyrus; (3) cortical gray matter: a thin band around the subcortical white matter gyri; and (4) deep gray matter: thalamus, globus pallidus, putamen, and head of the caudate nucleus. The five subcortical white matter regions in the gyri were combined to yield mean diffusion parameters, as were the five cortical gray matter regions.

ROIs were drawn on the slice of the FA map where the structures were visualized to be at their thickest, with the exception of the globus pallidus, putamen, and caudate for which the ROIs were placed initially on the non-diffusion-weighted images ($b = 0$ s/mm^2). Using image analysis software (MRVision, Winchester, MA), the structure in question was outlined following its contours. However, the corona radiata, centrum semiovale, globus pallidus, putamen, and caudate had small ROIs placed on central regions of the structure. ROIs were then translated onto the corresponding FA and Trace/3 ADC maps. ROIs were also translated onto the eigenvalue maps of all structures that showed significant correlation of FA with age in the children. Where appropriate left and right measurements were taken separately. To avoid inclusion of cerebrospinal fluid (CSF) in the ROIs, non-diffusion-weighted images and Trace/3 ADC maps were used to better visualize and avoid the CSF spaces. The ROI method was chosen so as to avoid any problems due to normalization of the brain into stereotactic space, and so that summary data on entire brain structures could be analyzed as opposed to a voxel by voxel

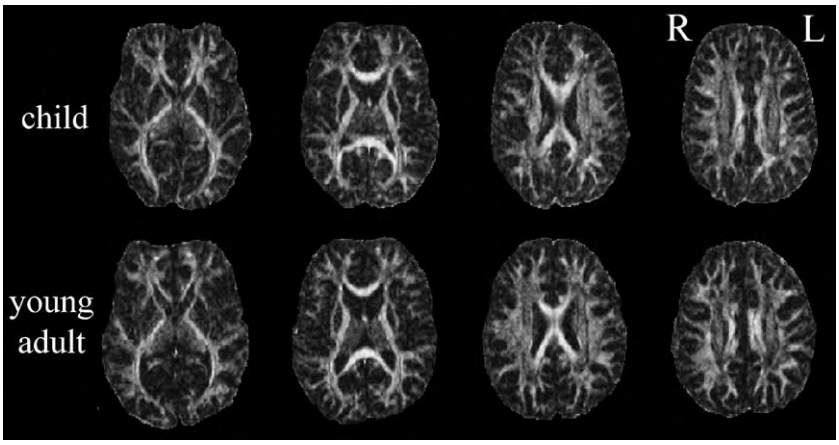

Fig. 1. Representative fractional anisotropy (FA) maps of four transverse slices of a 12-year-old female volunteer (above) and a 26-year-old male volunteer (below).

analysis. Furthermore, the structures we analyzed are readily identified on the 2D MR images.

Statistical analysis

Left/right asymmetry

Left and right FA and Trace/3 ADC values were compared using paired *t* tests (significant with $P < 0.05$). Where no significant left/right differences exist, the values are averaged for all further analyses. Absolute differences of less than 0.01×10^{-3} mm^2/s for Trace/3 ADC or 0.01 for FA between left and right are not reported.

Correlation analysis

Linear regression was performed for both FA and Trace/3 ADC versus age within the 8- to 12-year age range of the children and within the 21- to 27-year age range of the young adults (significant with $P < 0.05$).

Group analysis

Unpaired *t* tests were performed to compare each brain region individually between the child group and the young adult group (significant with $P < 0.05$).

ROI reliability

Three subjects (aged 17, 22, and 23 years) were scanned on four different occasions over the course of 4 months. ROIs were drawn in the genu, corona radiata, thalamus, and caudate. The mean FA values for each structure for each of the three subjects (mean over 4 scans ± SD) were as follows: genu of the corpus callosum (0.78 ± 0.01, 0.76 ± 0.01, 0.84 ± 0.02), corona radiata (0.61 ± 0.02, 0.65 ± 0.02, 0.68 ± 0.01), thalamus (0.30 ± 0.01, 0.34 ± 0.03, 0.34 ± 0.02), and head of the caudate nucleus (0.20 ± 0.01, 0.20 ± 0.02, 0.23 ± 0.02). These intra-subject standard deviations are in general less than the inter-subject variability

Table 1
Group analysis statistics for fractional anisotropy (FA)—children versus young adults

Region	FA, children ($N = 32$) (8–12 years) (mean ± SD)	FA, young adults ($N = 28$) (21–27 years) (mean ± SD)	*P*	Difference (%)
White matter				
Genu of corpus callosum	0.70 ± 0.05	0.78 ± 0.03	<0.0001	11
Splenium of corpus callosum	0.76 ± 0.03	0.81 ± 0.03	<0.0001	7
Anterior limb of internal capsule	0.58 ± 0.04	0.66 ± 0.05	<0.0001	14
Posterior limb of internal capsule	0.66 ± 0.03	0.70 ± 0.03	<0.0001	6
External capsule	0.47 ± 0.03	0.51 ± 0.03	<0.0001	9
Corona radiata	0.56 ± 0.04	0.62 ± 0.04	<0.0001	11
Centrum semiovale[a]	0.47 ± 0.02	0.46 ± 0.05	0.15	–
Subcortical WM of gyri	0.44 ± 0.06	0.49 ± 0.06	<0.0001	11
Gray matter				
Thalamus	0.31 ± 0.03	0.33 ± 0.03	0.007	7
Globus pallidus	0.25 ± 0.02	0.28 ± 0.04	<0.0001	12
Putamen	0.15 ± 0.02	0.17 ± 0.02	<0.0001	13
Caudate	0.16 ± 0.02	0.21 ± 0.03	<0.0001	31
Cortical GM	0.18 ± 0.03	0.18 ± 0.03	0.94	–

[a] Left/right combined value is presented for centrum semiovale: left FA 0.48 ± 0.03 children, left FA 0.47 ± 0.05 young adults, $P = 0.30$; right FA 0.46 ± 0.03 children, right FA 0.44 ± 0.05 young adults, $P = 0.02$.

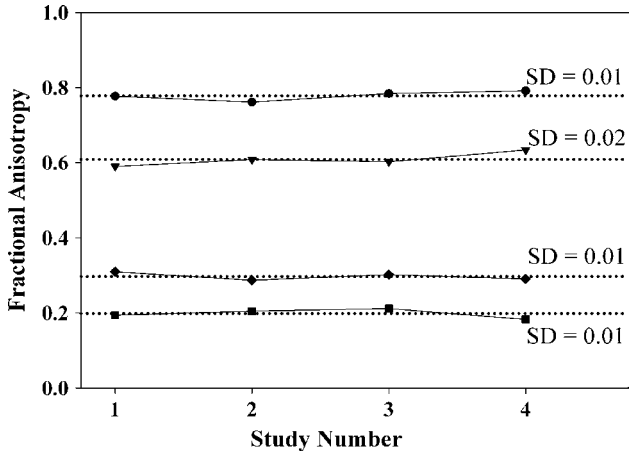

Fig. 2. Variability of ROI measurements of fractional anisotropy for one subject over 4 scans taken within a period of 4 months for the genu of the corpus callosum (FA range = 0.76–0.79, SD = 0.01), corona radiata (0.59–0.63, 0.02), thalamus (0.29–0.31, 0.01), and head of the caudate nucleus (0.18–0.21, 0.01). The dashed lines represent the mean of the 4 measurements. The variability shown in this graph is very small, suggesting a high level of consistency in both imaging and ROI methods.

(Table 1). Fig. 2 shows the variability of all four regions for one of the subjects (22-year-old male).

Results

Left/right asymmetry

Overall, there was very little hemispheric asymmetry in either Trace/3 ADC or FA, and even when asymmetry was present, its magnitude was small. FA was greater on the left in the anterior limb of the internal capsule (mean over 32 volunteers ± SD: left 0.59 ± 0.05, right 0.57 ± 0.05, $P = 0.05$) and centrum semiovale (left 0.48 ± 0.03, right 0.46 ± 0.03, $P = 0.05$) in the 8- to 12-year-old children. In the young adults, the centrum semiovale also showed leftward asymmetry of FA (mean over 28 volunteers ± SD: left 0.47 ± 0.05, right 0.44 ± 0.05, $P = 0.0001$), but the globus pallidus had rightward asymmetry (left 0.27 ± 0.04, right 0.29 ± 0.05, $P = 0.002$).

Correlation analysis (within 8–12 years and within 21–27 years)

Significant increases of FA were seen in 5 of 13 regions, namely, the genu of the corpus callosum ($P = 0.002$, $r = 0.54$), splenium of the corpus callosum ($P = 0.02$, $r = 0.42$), corona radiata ($P = 0.02$, $r = 0.40$), putamen ($P = 0.05$, $r = 0.35$), and head of the caudate nucleus ($P = 0.0007$, $r = 0.57$) (Fig. 3a). No significant decreases of FA were seen with age in the children. On the other hand, a significant decrease in Trace/3 ADC was seen in 9 of 13 brain regions in children over this 5-year age span, with the exception of the genu of the corpus callosum, posterior limb of the internal capsule, thalamus, and cortical gray matter (Figs. 3b–d). In young adults, there was very little change within the larger time span of 21–27 years of age and it was limited to a significant increase of Trace/3 ADC in the left globus pallidus ($r = 0.41$, $P = 0.03$) and a significant increase of FA in the right centrum semiovale ($r = 0.44$, $P = 0.02$).

The eigenvalues of the diffusion tensor were evaluated for correlation with age in the five brain regions that had significant linear increases of FA over the 8- to 12-year-old age range (Fig. 4). In the genu of the corpus callosum, splenium of the corpus callosum, corona radiata, and head of the caudate nucleus, the "parallel" diffusivity (λ_1) stayed constant, whereas the "perpendicular" diffusivity (λ_2 and λ_3) decreased significantly ($P < 0.01$) from 8 to 12 years. In contrast, all three eigenvalues decreased significantly for the putamen with age over 8–12 years ($P < 0.001$).

Group analysis (8–12 years versus 21–27 years)

When comparing the children to the young adults, increases in FA were seen in 11 of 13 structures; however, a decrease of FA was seen in the right centrum semiovale (Table 1). The trend of decreasing Trace/3 ADC, as seen in the correlational analysis, was seen in 12 of 13 structures ($P < 0.01$, absolute difference ranging from 3% to 10%) (Table 2). The cortical gray matter showed no trends for either FA or Trace/3 ADC.

Putting together the correlation and group analyses, FA is observed to continually increase from 8 years to young adulthood in 5 of 13 structures whereas Trace/3 ADC continues to drop over this age range in 9 of 13 structures (Fig. 5).

Discussion

High-resolution diffusion tensor imaging in 60 healthy subjects has demonstrated maturational changes in the brain throughout late childhood (8–12 years) and in the progression towards young adulthood (21–27 years). The timing of these changes in the water diffusion parameters implies a marked development of regional-specific brain microstructure from pre-adolescence to young adulthood.

Left/right asymmetry was seen in very few structures. It has been suggested that this difference may be due to coherence of fiber bundles as opposed to differences in myelination (Klingberg et al., 1999). The most interesting left/right difference was seen in the centrum semiovale, with higher FA values on the left side, not only in the children, but also in the young adults. In fact, the left/right difference became more pronounced and more significant with age, increasing from 3% ($P = 0.05$) to 7% ($P = 0.0001$) due to a unilateral reduction of FA between childhood and young adulthood in the right centrum. However, the interpretation of this asymmetry in a complex fiber-crossing region such as the centrum semiovale is uncertain. Significant left/right differences were reported in the superior longitudinal fasciculus in a recent study (Büchel et al., 2004) with higher FA in the left hemisphere, similar to our findings.

In the children (8–12 years), we saw widespread changes in mean diffusivity (i.e., Trace/3 ADC) and a smaller number of brain regions with changes in diffusion anisotropy (i.e., FA). Decreases in Trace/3 ADC were observed in 9 of 13 structures measured in the children in agreement with previous reports of reduced ADC with development (Schmithorst et al., 2002; Schneider et al., 2004). Increases of FA were observed in 5 of 13 structures, mainly in the central parts of the brain such as the genu and splenium of the corpus callosum, corona radiata, caudate nucleus, and putamen. The significant diffusion trends of these white matter regions in the 8- to 12-year-olds suggest that

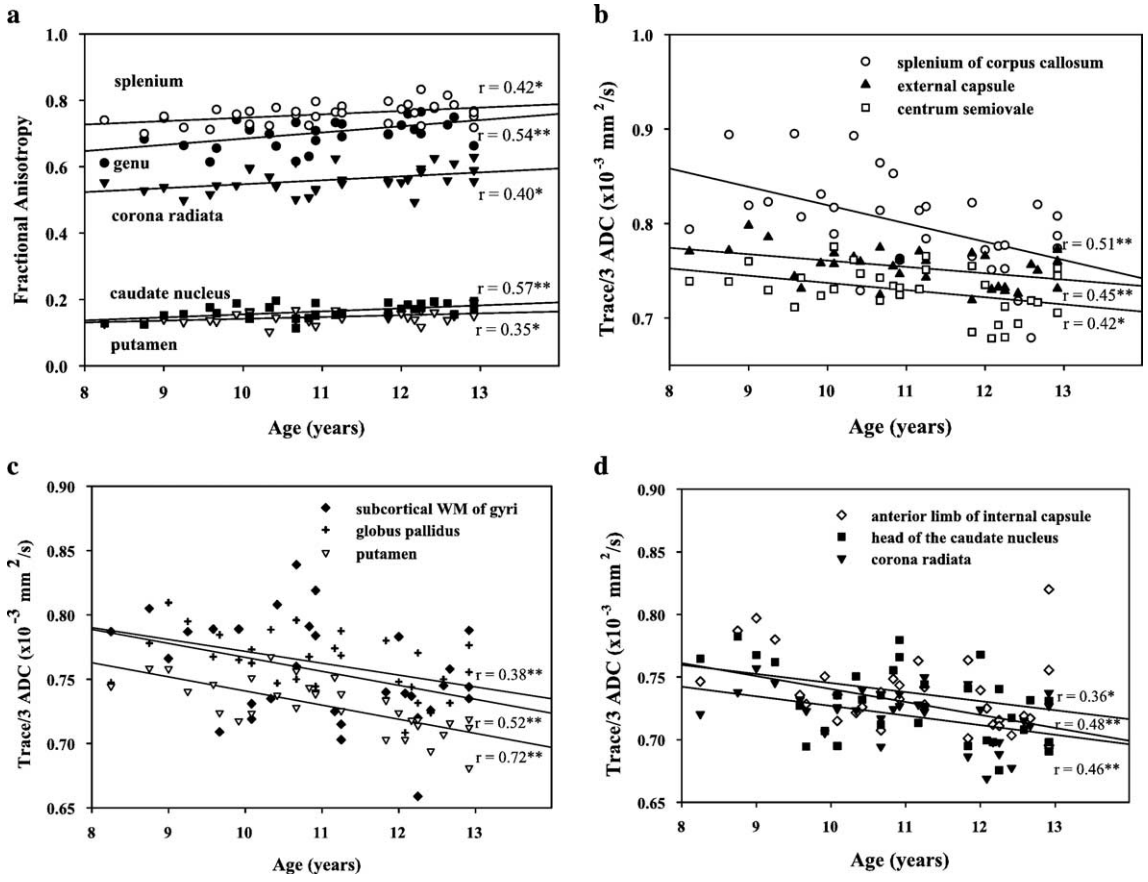

Fig. 3. Correlation trends within 8–12 years. Linear regression of FA and Trace/3 ADC values with age in the 8–12-year child age range. (a) Of the 13 distinct brain regions measured, positive correlations of FA were observed in five regions, listed from top to bottom: splenium of corpus callosum, genu of corpus callosum, corona radiata, head of the caudate nucleus, and putamen. Negative correlations of Trace/3 ADC were observed in nine regions, listed from top to bottom: (b) splenium of corpus callosum, external capsule, and centrum semiovale; (c) subcortical white matter in the gyri, globus pallidus, and putamen; (d) anterior limb of the internal capsule, head of the caudate nucleus, and corona radiata. Fewer regions of the brain demonstrate positive correlations of fractional anisotropy within the narrow 8–12-year-old age range than negative correlations of Trace/3 ADC (*$P < 0.05$, **$P < 0.01$).

diffusion MRI is more sensitive to underlying microstructural changes associated with brain maturation, since these same regions did not demonstrate "white matter density" changes on T1-weighted images (Paus et al., 1999), even though the age range in that study was greater at 4–17 years.

It is known that myelination follows a posterior–anterior progression with development, and that the projection fibers develop first followed by the commissural and finally associational fibers (Filley, 2001). We see changes in both projection fibers (e.g., internal capsule and corona radiata) as well as commissural fibers (corpus callosum) through childhood. It is of interest that the internal capsule is one of the first structures to myelinate in infancy, and that the posterior limb is known to myelinate much earlier than the anterior limb (Barkovich et al., 1988; Yakovlev and Lecours, 1967). This timing difference appears to agree with the greater change of FA in the anterior limb of the internal capsule than in the posterior limb of the internal capsule between childhood and young adulthood (Table 1). As well, it is of note that the corona radiata is made up of the projection fibers that radiate out of the brain stem via the internal capsule (Greenstein and Greenstein, 2000). The diffusion changes may be reflecting the continued development of the internal capsule out into the corona radiata in later childhood. Although the posterior limb of the internal capsule and corona radiata appears to be fully myelinated (i.e., highest myelin staining grade) by 2 years of age in autopsy studies (Brody et al., 1987), there are significant increases of FA due to axonal growth and/or myelination between childhood and young adulthood in these two structures.

The commissural fibers are known to develop next after the projection fibers, and in fact continued development of the corpus callosum through early adolescence has been described by a wave of growth from posterior to anterior in the corpus callosum (Thompson et al., 2000). The slope of FA increase is greater for the genu (0.02 FA units per year) than for the splenium (0.01 FA units per year), which would be consistent with the greater anterior development of the corpus callosum over this age span of 8–12 years (Fig. 3a). Also, the genu has a greater increase from childhood to adulthood for FA (Table 1) and a greater decrease for Trace/3 ADC (Table 2) than the splenium.

Eigenvalue analysis shows a reduction of diffusion perpendicular to the fiber tracts (λ_2 and λ_3), whereas diffusion parallel to the tracts (λ_1) is fairly constant, with the exception of the putamen over the range of 8–12 years. Hence increases in FA are not caused by an increase in the parallel eigenvalue, but rather by a decrease in the perpendicular eigenvalues. A greater reduction in the two perpendicular eigenvalues has been observed with maturation

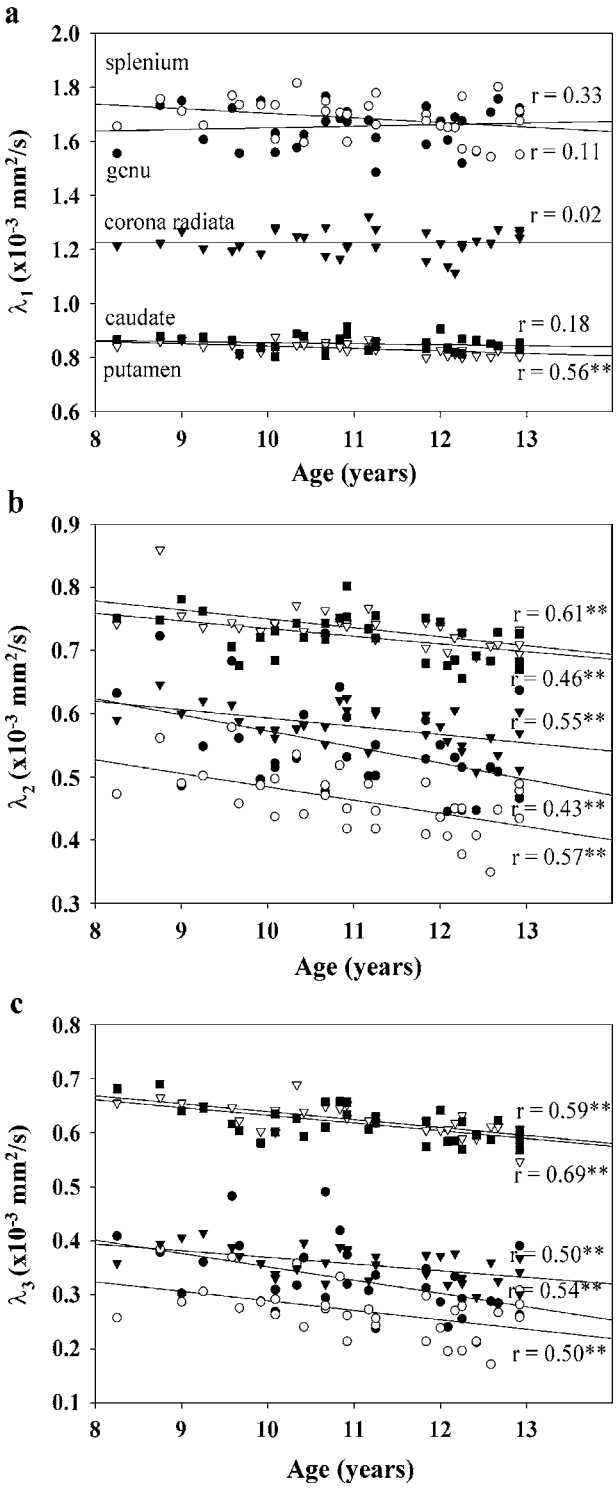

Fig. 4. Eigenvalue correlations within 8–12 years. In the five brain regions that showed a significant increase of fractional anisotropy over ages 8–12 years, linear regression of the three eigenvalues of the diffusion tensor with age demonstrates that (a) the parallel diffusivity (λ_1) is approximately constant in all structures except the putamen which has a small decline with age, (b and c) whereas the perpendicular diffusivity (λ_2, λ_3) decreases significantly with age in all five structures.

(between children of 1–10 years and young adults) in the frontal and parietal lobe white matter (Suzuki et al., 2003) as well as in the basal ganglia, internal capsule, and corpus callosum in children aged 31 gestational weeks to 11 years, with the majority of the change occurring in the first 2 years of life (Mukherjee et al., 2002). This observation of reduced perpendicular diffusivity is consistent with either an increase in the compactness or density of the fiber bundles and/or increased myelination.

In stark contrast to these changes, there were very few changes seen within 21–27 years of age. We saw an increase in Trace/3

Table 2
Group analysis statistics for mean diffusivity (Trace/3 ADC)—children versus young adults

Region	Trace/3 ADC, children (N = 32) (8–12 years) (mean ± SD), $\times 10^{-3}$ mm^2/s	Trace/3 ADC, young adults (N = 28) (21–27 years) (mean ± SD), $\times 10^{-3}$ mm^2/s	P	Difference (%)
White matter				
Genu of corpus callosum	0.83 ± 0.06	0.75 ± 0.03	<0.0001	−10
Splenium of corpus callosum	0.80 ± 0.05	0.75 ± 0.03	<0.0001	−6
Anterior limb of internal capsule	0.74 ± 0.03	0.70 ± 0.02	<0.0001	−5
Posterior limb of internal capsule	0.74 ± 0.02	0.72 ± 0.02	0.004	−3
External capsule	0.75 ± 0.02	0.73 ± 0.02	<0.0001	−3
Corona radiata	0.72 ± 0.02	0.69 ± 0.02	<0.0001	−4
Centrum semiovale	0.73 ± 0.03	0.71 ± 0.03	0.01	−3
Subcortical WM of gyri	0.77 ± 0.04	0.73 ± 0.05	<0.0001	−5
Gray matter				
Thalamus	0.78 ± 0.03	0.74 ± 0.02	<0.0001	−5
Globus pallidus	0.76 ± 0.02	0.73 ± 0.03	<0.0001	−4
Putamen	0.73 ± 0.02	0.69 ± 0.02	<0.0001	−6
Caudate	0.73 ± 0.03	0.66 ± 0.03	<0.0001	−10
Cortical GM	0.82 ± 0.04	0.82 ± 0.05	0.44	–

ADC in the left globus pallidus, which could be an indication of the increasing trends in mean diffusivity previously reported with aging in adulthood (Abe et al., 2002; Bhagat and Beaulieu, 2004; Pfefferbaum et al., 2000). We also saw an increase of FA in the right centrum semiovale. This was not paralleled in the left centrum semiovale, nor was it observed in the children. However, the centrum semiovale is a complex structure composed of numerous crossing projectional, commissural, and associational fibers. Since standard DTI cannot resolve crossing fibers within a voxel, the pattern of FA changes (or lack thereof), including a decrease of FA in the right centrum between childhood and young adulthood followed by an increase of FA in the same region during young adulthood, may be artificial and misleading for the centrum semiovale. More sophisticated methods of resolving multiple crossing fibers in a single voxel such as Q-Ball imaging (Tuch, 2004), which uses a greater number of diffusion-encoding directions and specific post-processing methods, may be necessary to detect the complicated growth patterns within areas such as the centrum semiovale. However, it is important to note that when considering an increase in the number of encoding directions in a DTI sequence, the duration of the scan must be considered, particularly when imaging children.

Although most of the gray and white matter structures we measured did not show any change in FA over 21–27 years (only exception was increase in right centrum semiovale), histological studies have provided evidence that associative cortical regions of the human brain continue to myelinate well beyond childhood (Benes et al., 1994). However, we did not measure the associational fibers (e.g., U fibers) since our 2D region-of-interest analysis targeted readily identifiable areas that are straightforward to outline, primarily deep central white matter, such as the corpus callosum or internal capsule. It would be more difficult to outline the various associational fibers on the 2D images and then measure robust, reproducible FA values. Future analysis using three-dimensional fiber tracking techniques could be useful for the assessment of these peripheral white matter fibers (Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999). Furthermore, it is possible that on-going changes in myelination and axonal growth do not manifest themselves as large enough changes of FA with age to detect with the 6-direction DTI method used in our study at 1.5 T. DTI obtained with higher angular resolution (i.e., more diffusion-sensitizing gradient directions), better spatial resolution, and larger static magnetic field could both improve the accuracy and reduce the variability of the diffusion parameters.

Group analysis of the diffusion parameters showed that much has changed between childhood and young adulthood. More widespread changes were seen in both Trace/3 ADC and FA than was seen in either correlational analysis. To summarize, 11 of 13 structures showed increases in FA and 12 of 13 structures showed decreases in Trace/3 ADC. Fig. 5 shows the regions in which developmental changes were apparent. Red regions show increases both within 8–12 years as well as between childhood and young adulthood. Yellow regions show increases only between childhood and young adulthood but do not demonstrate any measurable changes within 8–12 years. Due to the fact that more regions are developing between childhood and young adulthood (i.e., only the genu of the corpus callosum, splenium of the corpus callosum, corona radiata, putamen, and head of the caudate nucleus show FA changes within childhood as well as young adulthood, whereas the posterior limb of the internal capsule, anterior limb of the internal capsule, external capsule, subcortical white matter of the gyri, thalamus, and globus pallidus all show FA changes only between childhood and young adulthood), we believe that more significant and widespread brain changes are occurring throughout the teenage years between our child and young adult groups. These temporal differences in maturation are highlighted in Fig. 5 by the fact that there are more yellow regions than red regions on the FA maps. In contrast to FA, note that the Trace/3 ADC continually decreases through childhood and adolescence, shown by more red regions in Fig. 5. These findings confirm those of a previous T1-weighted imaging study that reported significant brain growth between adolescence and adulthood, but very little growth between childhood and adolescence (Sowell et al., 2001).

No significant changes were seen in the diffusion properties of cortical gray matter, in either anisotropy or mean diffusivity. Hence, either the structure of the cortex is fairly static by the time puberty is reached, or DTI is insufficient for detecting microstructural changes

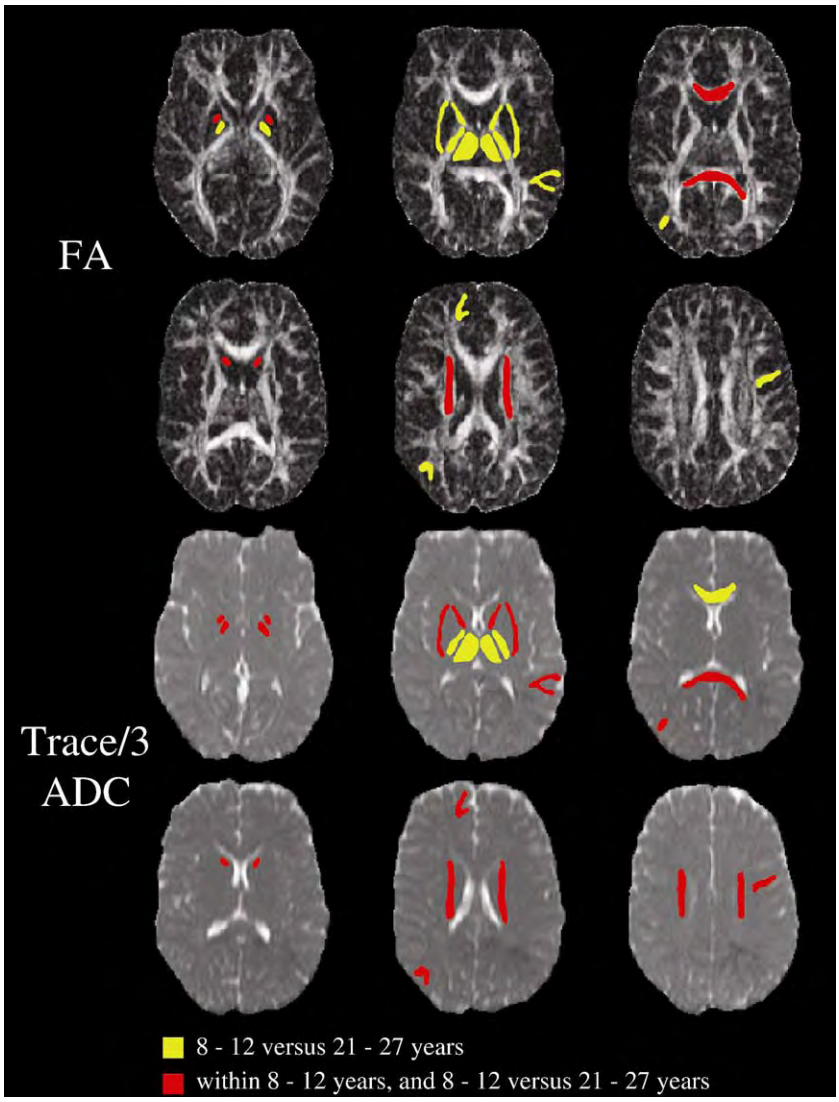

Fig. 5. Regional changes in maturation. FA and Trace/3 ADC maps of six slices in a 12-year-old female volunteer. ROIs are drawn as per the analysis method. Red regions show both significant correlations within 8–12 years and significant differences between childhood and young adulthood. Yellow regions only show significant changes between childhood and young adulthood, suggesting development during adolescence. Note that the splenium of the corpus callosum, corona radiata, head of the caudate nucleus, and putamen show continued changes with age for both FA and Trace/3 ADC (i.e., red on both maps). The remaining structures demonstrate different progression of FA and Trace/3 ADC.

that are related to volume increases/decreases that occur in cortical gray matter over this time frame (Giedd et al., 1999; Sowell et al., 2004). However, some of the largest changes seen were in the deep (subcortical) gray matter. Increases of FA were seen in the caudate head and the putamen within 8–12 years of age. Between childhood and adulthood all deep gray matter regions measured showed large increases of FA: 7% increase in the thalamus, 12% in the globus pallidus, 13% in the putamen, and 31% in the head of the caudate nucleus. Consistent with our findings, a small linear increase in the head of the caudate nucleus and the lentiform nucleus (comprising the putamen and globus pallidus) was reported (Mukherjee et al., 2001) as the only region which showed continued increase over 1 day to 11 years. There is a paucity of gray matter DTI studies due to low FA values (<0.25 FA units); however, it is clear from our data that major changes are occurring that are detectable using DTI. The DTI findings agree with 3D T1-weighted MRI studies that have demonstrated marked gray matter density changes in the striatum, primarily in the putamen and the globus pallidus, between adolescence (12–16 years) and young adults (23–30 years) (Sowell et al., 1999). These findings could be related to an increase in motor coordination with maturation or cognitive development associated with brain regions that are linked to these deep gray matter structures. Higher density, more coherent organization, and/or a greater degree of myelination of fibers (i.e., axons) going into and out of these gray matter relay stations could all contribute to the increases of FA. Small increases of anisotropy in the basal ganglia have been attributed previously to internal white matter pathways (Mukherjee et al., 2001), as opposed to changes of the diffusion parameters of the gray matter neurons.

In conclusion, non-invasive diffusion tensor magnetic resonance imaging of water demonstrates that many regions of the brain continue to develop through late childhood. Relative to the younger age range (8–12 years), a greater number of brain regions demonstrate increases of diffusion anisotropy and decreases of

mean diffusivity during the adolescent period in the transition from childhood to young adulthood suggesting a progressive pattern of myelination/axon growth during this critical time period of neurodevelopment.

Acknowledgments

Support provided by Networks of Centres of Excellence (NCE)—Canadian Language and Literacy Research Network (www.cllrnet.ca), Alberta Heritage Foundation for Medical Research (AHFMR) (CB), Canadian Institutes of Health Research (CIHR) (CB), and Natural Sciences and Engineering Research Council of Canada (NSERC) (LS). MRI infrastructure provided by AHFMR, Canada Foundation for Innovation, Alberta Science and Research Authority, and the University Hospital Foundation. We thank Yusuf Bhagat and Simon McCrea for help in the early stages of this project.

References

Abe, O., Aoki, S., Hayashi, N., Yamada, H., Kunimatsu, A., Mori, H., Yoshikawa, T., Okubo, T., Ohtomo, K., 2002. Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. Neurobiol. Aging 23, 433–441.

Barkovich, A.J., Kjos, B.O., Jackson Jr., D.E., Norman, D., 1988. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. Radiology 166, 173–180.

Basser, P.J., 1995. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed. 8, 333–344.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system—A technical review. NMR Biomed. 15, 435–455.

Benes, F.M., Turtle, M., Khan, Y., Farol, P., 1994. Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. Arch. Gen. Psychiatry 51, 477–484.

Bhagat, Y.A., Beaulieu, C., 2004. Diffusion anisotropy in subcortical white matter and cortical gray matter: changes with aging and the role of CSF-suppression. J. Magn. Reson. Imaging 20, 216–227.

Brody, B.A., Kinney, H.C., Kloman, A.S., Gilles, F.H., 1987. Sequence of central nervous system myelination in human infancy: I. An autopsy study of myelination. J. Neuropathol. Exp. Neurol. 46, 283–301.

Büchel, C., Raedler, T., Sommer, M., Sach, M., Weiller, C., Koch, M.A., 2004. White matter asymmetry in the human brain: a diffusion tensor MRI study. Cereb. Cortex 14, 945–951.

Chenevert, T.L., Brunberg, J.A., Pipe, J.G., 1990. Anisotropic diffusion in human white matter: demonstration with MR techniques in vivo. Radiology 177, 401–405.

Conturo, T.E., Lori, N.F., Cull, T.S., Akbudak, E., Snyder, A.Z., Shimony, J.S., McKinstry, R.C., Burton, H., Raichle, M.E., 1999. Tracking neuronal fiber pathways in the living human brain. Proc. Natl. Acad. Sci. U. S. A. 96, 10422–10427.

Courchesne, E., Chisum, H.J., Townsend, J., Cowles, A., Covington, J., Egaas, B., Harwood, M., Hinds, S., Press, G.A., 2000. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. Radiology 216, 672–682.

Filley, C.M., 2001. The Behavioral Neurology of White Matter. Oxford Univ. Press, Oxford.

Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nat. Neurosci. 2, 861–863.

Greenstein, B., Greenstein, A., 2000. Color Atlas of Neuroscience: Neuroanatomy and Neurophysiology. Theime, Stuttgart.

Jones, D.K., Simmons, A., Williams, S.C., Horsfield, M.A., 1999. Non-invasive assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. Magn. Reson. Med. 42, 37–41.

Klingberg, T., Vaidya, C.J., Gabrieli, J.D., Moseley, M.E., Hedehus, M., 1999. Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. NeuroReport 10, 2817–2821.

Le Bihan, D., 2003. Looking into the functional architecture of the brain with diffusion MRI. Nat. Rev., Neurosci. 4, 469–480.

McKinstry, R.C., Mathur, A., Miller, J.H., Ozcan, A., Snyder, A.Z., Schefft, G.L., Almli, C.R., Shiran, S.I., Conturo, T.E., Neil, J.J., 2002. Radial organization of developing preterm human cerebral cortex revealed by non-invasive water diffusion anisotropy MRI. Cereb. Cortex 12, 1237–1243.

Miller, J.H., McKinstry, R.C., Philip, J.V., Mukherjee, P., Neil, J.J., 2003. Diffusion-tensor MR imaging of normal brain maturation: a guide to structural development and myelination. Am. J. Roentgenol. 180, 851–859.

Mori, S., Crain, B.J., Chacko, V.P., van Zijl, P.C., 1999. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann. Neurol. 45, 265–269.

Moseley, M., 2002. Diffusion tensor imaging and aging—A review. NMR Biomed. 15, 553–560.

Moseley, M.E., Cohen, Y., Kucharczyk, J., Mintorovitch, J., Asgari, H.S., Wendland, M.F., Tsuruda, J., Norman, D., 1990. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 176, 439–445.

Mukherjee, P., Miller, J.H., Shimony, J.S., Conturo, T.E., Lee, B.C., Almli, C.R., McKinstry, R.C., 2001. Normal brain maturation during childhood: developmental trends characterized with diffusion-tensor MR imaging. Radiology 221, 349–358.

Mukherjee, P., Miller, J.H., Shimony, J.S., Philip, J.V., Nehra, D., Snyder, A.Z., Conturo, T.E., Neil, J.J., McKinstry, R.C., 2002. Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. Am. J. Neuroradiol. 23, 1445–1456.

Neil, J., Miller, J., Mukherjee, P., Huppi, P.S., 2002. Diffusion tensor imaging of normal and injured developing human brain—a technical review. NMR Biomed. 15, 543–552.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D.L., Blumenthal, J., Giedd, J.N., Rapoport, J.L., Evans, A.C., 1999. Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283, 1908–1911.

Paus, T., Collins, D.L., Evans, A.C., Leonard, G., Pike, B., Zijdenbos, A., 2001. Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain Res. Bull. 54, 255–266.

Pfefferbaum, A., Sullivan, E.V., Hedehus, M., Lim, K.O., Adalsteinsson, E., Moseley, M., 2000. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. Magn. Reson. Med. 44, 259–268.

Schmithorst, V.J., Wilke, M., Dardzinski, B.J., Holland, S.K., 2002. Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. Radiology 222, 212–218.

Schneider, J.F., Il'yasov, K.A., Hennig, J., Martin, E., 2004. Fast quantitative diffusion-tensor imaging of cerebral white matter from the neonatal period to adolescence. Neuroradiology 46, 258–266.

Sowell, E.R., Thompson, P.M., Holmes, C.J., Jernigan, T.L., Toga, A.W., 1999. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat. Neurosci. 2, 859–861.

Sowell, E.R., Thompson, P.M., Tessner, K.D., Toga, A.W., 2001. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. J. Neurosci. 21, 8819–8829.

Sowell, E.R., Trauner, D.A., Gamst, A., Jernigan, T.L., 2002. Development of cortical and subcortical brain structures in child-

hood and adolescence: a structural MRI study. Dev. Med. Child Neurol. 44, 4–16.
Sowell, E.R., Thompson, P.M., Toga, A.W., 2004. Mapping changes in the human cortex throughout the span of life. Neuroscientist 10, 372–392.
Suzuki, Y., Matsuzawa, H., Kwee, I.L., Nakada, T., 2003. Absolute eigenvalue diffusion tensor analysis for human brain maturation. NMR Biomed. 16, 257–260.
Thompson, P.M., Giedd, J.N., Woods, R.P., MacDonald, D., Evans, A.C., Toga, A.W., 2000. Growth patterns in the developing brain detected by using continuum mechanical tensor maps. Nature 404, 190–193.
Tuch, D.S., 2004. Q-ball imaging. Magn. Reson. Med. 52, 1358–1372.
Yakovlev, P., Lecours, A., 1967. The myelogenetic cycles of regional maturation of the brain. In: Minkowski, A. (Ed.), Regional Development of the Brain in Early Life. Blackwell, Oxford.