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Journal

Brain Research, 1466

ISSN

1872-6240

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Publication Date

2012-05-24

Peer reviewed

Published in final edited form as:

Brain Res. 2012 July 23; 1466: 33–43. doi:10.1016/j.brainres.2012.05.035.

Development of white matter pathways in typically developing preadolescent children

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Abstract

The first phase of major neuronal rearrangements in the brain takes place during the prenatal period. While the brain continues maturation throughout childhood, a critical second phase of synaptic overproduction and elimination takes place during the preadolescent period. Despite the importance of this developmental phase, few studies have evaluated neural changes taking place during this period. In this study, MRI Diffusion Tensor Imaging data from a normative sample of 126 preadolescent children (59 girls and 67 boys) between the ages of 6 and 10 years were analyzed in order to characterize age-relationships in the white matter microstructure. Tract Based Spatial Statistics (TBSS) method was used for whole brain analysis of white matter tracts without a priori assumption about the location of age associated differences. Our results demonstrate significant age-associated differences in most of the major fiber tracts bilaterally and along the whole body of the tracts. In contrast, developmental differences in the cingulum at the level of the parahippocampal region were only observed in the right hemisphere. We suggest that these age-relationships with a widespread distribution seen during the preadolescent years maybe relevant for the implementation of cognitive and social behaviors needed for a normal development into adulthood.

Keywords

Brain development; neurodevelopment; Diffusion Tensor Imaging; structural brain connectivity; preadolescent children

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1. Introduction

The initial phase of brain development takes place during the prenatal period, when the brain undergoes major neuronal rearrangements (Andersen, 2003). Subsequently, during the first two years of life the brain goes through a rapid growth with dramatic increases seen in axonal diameter and myelin sheath (Paus et al., 1999). Later, during the preadolescent period a critical second phase of brain development takes place (Andersen, 2003). During this period, significant overshoot of synapses and receptors followed by their pruning or competitive elimination are observed. The relevance of this phase in brain development has also been emphasized by Caviness *et al* (Caviness et al., 1996), noting that during preadolescence brain circuitry is fine-tuned to reach the cognitive performance of the adult brain. Despite the importance of this developmental stage, few studies have systematically investigated changes in the brain in this narrow age range.

Investigating normative changes in brain anatomy during childhood is important to understand the substrates of cognitive, behavioral and emotional maturation. Such knowledge may also aid in the assessment of aberrations in developmental trajectories that are associated with increased susceptibility for various cognitive and psychiatric disorders. For instance, alterations in brain morphology are associated with neuropsychiatric (depression, schizophrenia, anxiety disorders) and neurodevelopmental (autism, ADHD) disorders (Damsa et al., 2009; Del Arco and Mora, 2009; Garrett et al., 2008; Geuze et al., 2005; Kates et al., 2002; Kates et al., 2004; Koenigs and Grafman, 2009; Kyriakopoulos and Frangou, 2009; Mitchell et al., 2009; Shaw and Rabin, 2009; Szeszko et al., 2005; Verhoeven et al., 2010; White et al., 2008). The vulnerability hypothesis suggests that the risk of developing these disorders may be due, in part, to pre-existing alterations in brain morphology (Gilbertson et al., 2002; Paus et al., 2008), which has been supported in studies of patients prodromal for psychiatric disorders (Bhojraj et al., 2011; Witthaus et al., 2010).

We previously have shown trajectories of cortical maturation between 6 and 10 years of age (Muftuler et al., 2011). However, normative brain development requires coordinated refinements both in the gray matter (GM) and white matter (WM) for optimal cognitive, behavioral, emotional and motor development. There are studies that demonstrated an association between trajectories of brain WM maturation and intellectual performance (Schmithorst et al., 2005; Tamnes et al., 2010b). The observed positive relation between cognitive function and increasingly dense and ordered packing of WM fiber tracts supports the hypothesis that refined fiber organization is an essential developmental process related to cognitive performance. Therefore, it is additionally important to describe the changes in major white matter pathways.

MRI Diffusion Tensor Imaging (DTI) is a valuable tool to investigate age-associated changes in brain WM noninvasively because of its high sensitivity for the detection of changes in myelination, axonal density and axonal thickness (Beaulieu, 2002). Several groups have used DTI to study cerebral WM changes from childhood to early adulthood. Cascio et al (Cascio et al., 2007) published a comprehensive review on the developmental trends in WM development in different age ranges. Initial studies reported significant changes in all major white matter tracts up to 2 years of age. The majority of more recent studies investigated development changes in WM across a wide age range, spanning from childhood through adolescence or early adulthood or over the whole lifespan (Lebel et al., 2012). Some of the latter studies focused on a set of selected pathways (Eluvathingal et al., 2007) and others used voxel-based techniques to study age-related changes in the whole brain WM (Barnea-Goraly et al., 2005; Schmithorst et al., 2002). Despite variations in age ranges, acquisition parameters and analysis techniques, all published studies consistently reported increases in fractional anisotropy (FA) and decreases in mean diffusivity (MD)

values in various WM tracts as the brain matures from childhood to adulthood. However, there are some variations in the pathways reported and some inconsistencies exist especially regarding lateral asymmetries (Barnea-Goraly et al., 2005; Cascio et al., 2007; Paus et al., 1999; Provenzale et al., 2007; Schmithorst et al., 2002; Snook et al., 2005).

Although these studies demonstrate overall changes in the brain during the first two decades of life, several imaging studies have highlighted that maturational changes do not take place in all brain areas simultaneously (Kinney et al., 1988; Lebel et al., 2008; Sowell et al., 2004). For instance, cortical maturation was seen earlier in the posterior areas, progressing slowly to anterior areas (Sowell et al., 2004) and myelination occurs in proximal pathways before distal pathways and in central sites before poles (Kinney et al., 1988). Therefore, neurodevelopment should also be investigated in shorter epochs that span different phases of brain maturation to reveal age-dependent trajectories with more specificity. Only one DTI study primarily focused on WM development within the preadolescent period (8–12 years) and reported increases in FA and decreases in MD in a preselected set of WM pathways (Snook et al., 2005). The findings reported were limited to specific regions of interest in the corpus callosum, corona radiata, anterior limb of internal capsule, external capsule, and centrum semiovale and other major WM pathways were not investigated.

The objective of the present study is to: 1) determine if maturational changes in the preadolescent period are generalized; 2) identify which specific pathways show significant changes; 3) determine if there are differences between boys and girls in WM development. For this, DTI data from a large population of preadolescent children (ages 6 – 10) were analyzed in order to characterize age-relationships in the brain WM microstructure. The analysis was performed using the Tract Base Spatial Statistics (TBSS) technique (Smith et al., 2006) that tested age-related changes along all major WM tracts in the brain. This approach has several advantages over techniques that utilize average measurements inside pre-selected ROIs or fiber tracts. If the changes take place only in a segment of a tract, not uniformly along the entire tract, the results will be highly dependent on the location of the ROI. In such instances, averaging measurements inside the whole tract would also effectively reduce the magnitude of the age-related effects. The TBSS analysis, on the other hand, has the ability to show: 1) age-associated changes in the whole brain WM without any *a priori* assumptions about their locations; and 2) variations in the strength of age-associations in different segments of the tracts. Our results demonstrate significant age-associated differences in most of the major fiber tracts bilaterally between 6 and 10 years of age. However, there were three pathways where no maturational differences were observed or the differences were unilateral

2. Results

2.1. Age-associated differences in fiber tracts

Significant age-related increase in FA values and concurrent decrease in MD values were observed along Anterior Thalamic Radiation (ATR), Inferior Fronto-Occipital Fasciculi (IFO), Inferior Longitudinal Fasciculi (ILF), Superior Longitudinal Fasciculi, (SLF), Cortico-spinal Tracts (CST), Uncinate fasciculus (UF) and parts of Cingulum (CG). In contrast, a significant decrease in MD without any discernible difference in FA was observed along the right CG at the level of the ventromedial temporal regions. The typical findings of increasing FA and decreasing MD with age were not observed in the corpus callosum (CC) and fornix.

Figure 1 illustrates these results where the T1 weighted MNI152 standard brain was used as the background and each fiber track is overlaid in green. Then the whole-brain statistical maps were masked by each fiber track to illustrate the statistically significant age-

relationships in that particular track. The p-value maps of age-associated differences in FA and MD are overlaid in hot (red-yellow) and cold (blue-cyan) colors, respectively (see colorbars). Note that the color of statistical maps represents the strength of age-associated differences in different segments of the fiber tract. This type of illustration highlights if a particular segment of a fiber tract demonstrates stronger association with age than other parts.

For each subject the mean FA and MD values in the seven fiber tracts shown in figure 1 were calculated in order to quantify overall age-associated differences in those fasciculi. The mean FA and MD values were plotted against age in figure 2 for each one of these fiber tracts. The linear trend lines were also included in each plot to demonstrate the variations with age. The slopes of these trend lines are an indication of the rate of microstructural changes in those fiber tracts and the y-intercept of each trend line provides an evidence of how mature the tract was at age 6. The age-associated differences were similar in general in all pathways and no statistically significant differences were found between slopes of trend lines for different tracts ($F=0.21$, $p=0.974$ for FA plots and $F=0.23$, $p=0.966$ for MD plots). Similarly, differences between initial MD values across tracts were not significant but there was a subtle trend ($F=2.01$, $p=0.062$). The initial values of MD at age 6 varied between $0.81 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.89 \times 10^{-3} \text{ mm}^2/\text{s}$, with CST having the lowest and ILF the highest values. On the other hand, there were statistically significant differences in initial FA values of different tracts ($F=28$, $p=0.0000$). Figure 2 illustrates that the CST has the highest initial FA value (intercept at 0.51) and fastest rate of increase (slope of 0.004). ATR, IFO, ILF, SLF, CG and UF shared initial values at age 6 (0.39 – 0.43) but ATR, IFO, ILF and CG had slightly higher slopes (0.0032 – 0.0034) compared to SLF and UF (0.0026 – 0.0029). While these estimates cannot be directly related to any physiological phenomenon, they could be an indication of tract's maturity at the beginning and rate of its development in this age range.

The means and standard deviations of FA and MD values for each fiber tract across all subjects were also calculated and are presented in table 2. The percentage change per year in FA and MD values were also calculated by dividing the slopes of fitted trend lines in figure 2 by the respective mean FA and MD values, which are also listed in table 2. The comparison between FA and MD values for each specific pathway provided interesting results since the proportion between the two values varied among pathways. For instance, CST has the highest mean FA and the lowest mean MD values compared to all other tracts. These results on the differential between MD and FA suggest that the CST fiber tracts are probably the most densely packed fasciculus at this developmental stage. In addition, the temporal portion of the CG in the right side showed differences only in MD but not FA maybe suggesting a myelination process.

2.2. Sex differences

Age associated differences in FA or MD did not significantly differ by sex. The statistical maps of sex differences did not contain any voxels that survived a threshold of $p=0.05$ (corrected for multiple comparisons using family-wise error rate. (Flitney and Jenkinson)).

3. Discussion

In this study we have identified WM pathways with significant age-associated differences between 6 and 10 years of age. These differences probably are the result of ongoing synaptogenesis as well as myelination, increase in axonal diameter and perhaps number of fibers, which are thought to play an important role in cognitive, behavioral and emotional development during childhood and adolescence (Paus et al., 1999). Changes in WM during the first two postnatal years and differences between children and adults have been well

characterized. Here we provide new information about important developmental changes in WM that occur during the preadolescent period

We have used both fractional anisotropy and mean diffusivity to analyze age-associated differences in the brain white matter tracts in our population of children. Typically, increasing FA values and decreasing MD values are associated with more densely packed axonal fibers and increased myelination in the WM tracts in the brain (Beaulieu, 2002). The data from our cohort showed this trend in major fiber pathways (CST, ATR, IFO, ILF, SLF, CG, UF). Moreover, all of the fasciculi followed similar rates of increase in FA and decrease in MD values, indicating that they undergo similar maturational changes. This observation was supported by the analysis of differences in slopes between tracts, which showed no statistically significant differences. As shown in figure 2 and table 2, FA values increased 0.63% to 0.79% per year. Similarly, MD values decreased 0.54% to 0.90% per year. There is substantial variation reflected in the high standard deviation, yet the trend of age-association is clearly demonstrated and the rate of change is in a relatively close range of 0.5% to 1% per year. This rate of change is comparable to changes observed during normal aging. For instance, Hsu et al (Hsu et al., 2010) reported 1.4% decrease in mean global FA between ages 30 and 50. On the other hand, the rate of change that we observed between 6 and 10 years is smaller compared to reported changes of 25% – 30% in FA during the first two postnatal years (McGraw et al., 2002). These findings are in accord with reported developmental changes, which occur at a much slower rate after 2 years age (Hermoye et al., 2006; Mukherjee et al., 2001).

In our study the typical findings of increasing FA and decreasing MD with age were not observed in the CC or fornix. Findings on age-associated changes in CC are mixed. Hermoye et al (Hermoye et al., 2006) described rapid changes of FA and fiber tract size in the CC in the first 12 months, followed by relative stability after 24 months. Similarly, Paus et al (Paus et al., 1999) reported positive but nonsignificant changes in the density of WM in CC between 4 and 17 years. These studies suggest that maturation of the CC occurs relatively early in development and are consistent with postmortem studies which indicate that myelination occurs in proximal pathways before distal pathways and in central sites before poles (Kinney et al., 1988). Our findings are in accord with these reports, where it can be expected that CC and fornix completed most of the maturational development during early childhood and changes between 6 and 10 years are not significant. On the other hand, Snook et al (Snook et al., 2005) noted subtle differences in the genu and splenium between 8 and 12 years, which we have not detected in our data using the TBSS technique.

Another interesting finding was that, along the cingulum at the level of the parahippocampal region there were no discernible age-associated differences in FA values while MD values decreased significantly. There have been reports of changes in MD without a noticeable change in FA values (Acosta-Cabronero, 2009). This is possible if the microstructural changes such as increased myelination and axonal density in the fiber tract lead to a more restricted diffusion in all directions so that the characteristic of anisotropy in the voxel is preserved but water molecules have a much smaller volume to diffuse. It has been reported by several groups (see list in (Eluvathingal et al., 2007) that MD is more sensitive to developmental changes in WM than FA. This can be due to the fact that myelination might decrease MD without affecting FA.

In our cohort, an age-associated difference was detected in a seemingly large variety of pathways between the ages of 6 and 10 years. Differences were detected from the corticospinal pathway traditionally associated with the voluntary control of movements to pathways associated with complex cognitive functions (like the SLF) or emotional behaviors (CG). Previous reports have described developmental changes in some of these pathways

(CST, ATR, SLF) when comparing children to young adults (Barnea-Goraly et al., 2005; Snook et al., 2005; Tamnes et al., 2010b) suggesting some continuity throughout development. Other pathways detected in this study, have not been identified as such (CG, IFO, ILF, UF) even though global changes in the “ventral visual stream” have been previously reported (Barnea-Goraly et al., 2005).

It is striking and potentially highly significant that all of pathways showing developmental changes during the preadolescent period involve connectivity with the frontal and the temporal lobules. For instance, ATR connects the anterior thalamus with prefrontal areas. IFO is a fiber pathway between occipital and frontal regions. The SLF is a major pathway between superior temporal/parietal regions and prefrontal areas. The major component of the CST runs between motor regions in the frontal lobule and the brain stem and spinal cord. The UF connects the temporal pole and parahippocampal regions with orbitofrontal areas. The ILF (as described by Lennart Heimer, (Heimer, 2007) connects the occipital and the temporal lobules whereas the cingulum is a complex collection of white matter fibers that links the cingulate cortex with a large variety of areas including the ventromedial temporal regions.

The increase in connections to frontal and temporal areas is paralleled by the rapid development of executive and language functions in preadolescent children (McNealy et al., 2011). Indeed recent evidence suggests that these two critical cognitive functions follow similar developmental trajectories (Wilbourn et al., 2011). During preadolescence, children display major increases in verbal working memory (Brocki and Bohlin, 2004); goal-directed behavior (Anderson et al., 2001); response inhibition, selective attention (Klimkeit et al., 2004); and strategic planning and organizational skills (De Luca et al., 2003; Luciana and Nelson, 2002). Our DTI findings suggest age-associated refinements in the axonal connections to frontal and temporal areas, which are consistent with the evolution of cognitive abilities observed in preadolescent children.

Interestingly, the maturation of the frontal and the temporal lobules continues through young adulthood. Although individual sub-regions have been associated with a large variety of cognitive and limbic functions, globally, they all can be grouped with higher cognitive functions associated to social cognition (Adolphs, 2001; Frith, 2008; Olsson and Ochsner, 2008; Rizzolatti and Fabbri-Destro, 2008; Uddin et al., 2007). The only pathway that superficially may not fit this model is the CST. However, the involvement of the CST in supporting complex behaviors is not surprising because it not only represents the common motor output for the whole cortical system, but also its origin includes primary areas and association motor areas like the supplementary motor region, CG motor and the lateral premotor regions which are one of the cortical regions most developed through phylogeny (Jerison et al., 2001). Hence we suggest that the motor implementation of complex social behaviors is mediated by similarly complex motor regions (premotor, supplementary motor or cingulate motor) in the interface between cognitive and emotional regions.

It is also worth noting that the age-associated differences in all but one WM fiber tracts had hemispheric symmetry and the effects were seen along the majority of the tract body. The only exception was the CG. This fiber track had hemispheric symmetry at the level of frontal, parietal and occipital regions but not on the right side at the level of the ventromedial temporal region. This right-left and MD-FA dissociations in the temporal portion of the CG are not easy to interpret. One of the main targets of the ventromedial portion of the CG is the medial temporal cortices (including the entorhinal cortex) that have a late maturational process well into young adulthood (Insausti et al., 2010). In consequence, changes in MD alone could suggest a progressive myelination process in the path projecting to a late maturing region. In terms of lateralization, right lateralization has been shown in

adults for FA (de Groot et al., 2009), cingulate sulcus variance (Watkins et al., 2001) and path topology (Gong et al., 2005). Functional significance of this lateralization is hard to ascertain since during development the strength of structural connectivity does not seem to have a bearing in the weight of functional connectivity (Supekar et al., 2010).

Analysis of sex differences in age-relationship in WM tracts did not reveal any statistically significant results. A similar finding was reported for a larger age span (between 6 and 17 years) by Eluvathingal et al (Eluvathingal et al., 2007) where they used diffusion tensor tractography (DTT) to study the effects of age, sex differences and lateral asymmetries of 6 white matter pathways (arcuate fasciculus, ILF, IFO, UF, CST, and somato-sensory pathway). They also reported that the sex differences were insignificant in WM development between childhood and adulthood.

The findings reported here, focusing on changes in brain white matter in typically developing preadolescent children, complement the findings of Snook et al., (Snook et al., 2005; Snook et al., 2007). In their cross-sectional study of preadolescent children (8–12 years) and young adults (21–27 years) they observed strong age-associated differences in some WM areas within preadolescent period, but effects were negligible in young adults, indicating that most of the WM maturation is completed by early adulthood. In children, they reported increases in FA in genu and splenium of CC and corona radiata and decreases in MD in the splenium of CC, anterior limb of internal capsule, external capsule, corona radiata and centrum semiovale. This investigation was limited to the ROIs in specific WM areas and did not consider major pathways to the frontal and temporal lobes. The whole brain approach applied in the present investigation provides new information about important changes in major pathways that have afferent and efferent connections to the frontal and temporal lobes (IFO, ILF, CG, SLF, and UF).

Most published studies have reported trajectories of gray and white matter maturation across larger age spans, such as from childhood to adulthood (Barnea-Goraly et al., 2005; Eluvathingal et al., 2007; Lenroot and Giedd, 2006; Schmithorst et al., 2002; Snook et al., 2005; Sowell et al., 2004; Tamnes et al., 2010a). These studies demonstrated that cortical gray matter development is not simultaneous in all regions but rather it follows a posterior to anterior trajectory from childhood through adulthood (Lenroot and Giedd, 2006; Sowell et al., 2004). It was also shown that MRI-based measurements of development in gray and white matter structures follow different trends. Whereas the changes in volume of gray matter can be represented by a decrease over time or an inverted U, white matter changes show a progressive increase in FA. Assessment of these trajectories of brain development is important for characterizing typical brain development, and because this may provide information for determining risk for future neurodevelopmental disorders (Paus et al., 2008). For instance, there are studies that investigated the potential relationship between schizophrenia and aberrant brain development during childhood (Jaaro-Peled et al., 2009; Lewis and Levitt, 2002; Weinberger, 1987). Although it is generally agreed that various factors may play a role in the development of this disorder, their findings suggested that abnormal brain development during late childhood and adolescence could be one of the contributing factors. Specifically, aberrant synaptic elimination and disturbances in myelination during childhood especially in prefrontal and frontal areas were cited as potential factors in the onset of this disease (Jaaro-Peled et al., 2009). Since these processes continue through late childhood and mostly complete during young adulthood, the preadolescent period becomes important in the prodromal stages of this disease.

Therefore, the studies that establish the trajectories of typical brain development during childhood could aid in studies that explore relationships between aberrant development in certain brain regions during late childhood and various neuropsychiatric disorders that might

develop later in life. However deviations from normal developmental trajectories could be one of many complex factors that lead to mental health disorders and many individuals with similar aberrations from expected brains developmental trajectories might lead a life free from such disorders.

4. Methods

4.1. Subjects

A normative sample of 126 children (59 girls and 67 boys) between the ages of 74 and 129 months (~6 – 10 years) were scanned for this study (mean age 96.4 months). Descriptive Information for the study sample is presented in table 1. These children were from singleton intrauterine pregnancies born at one of two hospitals in the greater Los Angeles area (UC Irvine Medical Center, or Long Beach Memorial Medical Center) and were recruited from ongoing developmental studies. Our low risk sample had a stable neonatal course (Median Apgar = 9, Range 7 to 10) and did not have any congenital, chromosomal or genetic anomalies (e.g., trisomy 21) or neonatal illness (e.g., respiratory distress or sepsis). All participants presented normal neurologic findings at the time of enrollment. All children were typically developing and in the appropriate grade for their age. Twelve children were left-handed (Edinburgh Handedness Inventory (Oldfield, 1971)), reflecting the incidence in the general population. This study was approved by the Institutional Review Board for protection of human subjects. The children provided assent and guardians (mothers) gave informed consent for all aspects of the protocol.

4.2. MR Imaging protocol

MRI scans were acquired on a 3T Philips Achieva system. An 8-channel phased array head RF coil was used for this study. Tight padding was placed between the subject's head and the RF coil to minimize head motion. Ear protection was given to all children. To further increase compliance and reduce motion, children also wore headphones and watched a movie of their choice while in the scanner. Children were instructed to remain still while in the scanner and were asked to inform the research personnel in the room immediately if they wished to stop by using a squeeze ball that alerted the operator. Usually, the parents (with ear protection) stayed in the scanner room with the child to reduce anxiety and alert us if they observed any signs of distress.

In the beginning of a scanning session, the calibration and pilot scans were performed, which lasted less than a minute. These were followed by a high resolution T1 weighted scan for anatomical information using a 3D MPRAGE pulse sequence that covered the whole brain. The images were acquired in the sagittal orientation with FOV=240×240mm², 1mm³ isotropic voxel dimensions, 150 slices, TR=11ms, TE=3.3ms, inversion pulse delay =1100ms, flip angle=18°. No signal averaging and no SENSE acceleration were used. Acquisition time for the T1 weighted scan was 7 minutes. Finally the DTI scans were acquired using SE-EPI pulse sequence with 32 non-collinear gradient directions with b=800 and a single acquisition with b=0 for reference. The whole brain was covered with 60 axial slices using FOV=224×224mm² and 1.75×1.75×2mm³ voxel size, NEX=1. TR/TE=9290ms/55ms, SENSE=2.4. Total DTI scan time was 6 minutes and 50 seconds including high order shimming, de-ghosting and RF calibrations.

4.3. DTI data processing

Prior to any data processing and analysis, each subject's complete DTI image set was visually inspected for artifacts. DTI scans from ten subjects were found to contain motion related artifacts in a few of the slices in the diffusion weighted images; therefore, the data from those slices were excluded during DTI parameter fitting process. We have previously

inspected the impact of such data exclusion on the final FA and MD maps and found that the resulting errors were negligible if four DWI volumes were completely eliminated in a 32 direction data set (Muftuler, 2009). Since none of the DTI data sets contained more than four bad volumes, all data sets were included in the analysis after eliminating the slices with artifacts.

All DTI data processing and analysis were performed using FSL software (version 4.1) (<http://www.fmrib.ox.ac.uk/analysis/research/fdt/>) (Behrens et al., 2003; Smith et al., 2004). Before DTI parameter estimation, image registration was performed on each DTI image set using EDDYCORRECT function of FSL, which applies 12 parameter affine transformations to correct for distortions and misregistrations caused by eddy currents and head motion. This transformation applies 3 translations in 3 orthogonal directions (x, y, z), 3 rotations about the (x, y, z) axes, 3 zooms to expand or shrink the overall shape and 3 shears to correct any warping. The EDDYCORRECT script uses correlation ratio as the cost function for registration accuracy. The gradient direction vectors were corrected for head motion using `fdt_rotate_bvecs` function provided in FSL. Once the images were registered in a data set, a brain mask was created before DTI parameter estimation to exclude non-brain structures (e.g. facial muscles and eyes) from further analysis. This was done by Brain Extraction Tool (BET) software tool of the FSL. Then, FDT software of FSL was used to fit a diffusion tensor model at each voxel in the brain. After the eigenvectors and eigenvalues of the diffusion tensor model were estimated, Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps were generated for analysis.

FA and MD maps were prepared for statistical analysis using Tract Base Spatial Statistics (TBSS) software in FSL (Smith et al., 2006). TBSS software uses a nonlinear registration tool to align FA maps from all subjects into a template FA map. A subject-specific template was generated from the acquired data using tools available in TBSS (Smith et al., 2006). In the next step, the mean FA map was created and thinned to create a mean FA skeleton, which represents the centers of all WM tracts common to the group. In the final step, aligned FA maps from each subject were projected onto this skeleton.

4.4. Statistical analysis of DTI data

Once the skeletonized FA and MD maps were obtained, age-associated differences in FA and MD values in WM fibers across subjects were investigated using RANDOMISE function of FSL. RANDOMISE uses a permutation method (Nichols and Holmes, 2002), which tests the statistical significance of an experimental effect across subjects for correct labeling of the data against random re-labeling (permutations) of the same data. If there is no significant effect of the experimental variable, then each random re-labeling should result in equally plausible statistical distribution. In this approach, assumptions about the statistical distribution of the data are weak, unlike the parametric approaches.

Age-associated differences in WM tracts and sex differences were analyzed by setting up a General Linear Model (GLM) with age as the independent variable. However, instead of the classical parametric GLM analysis, the permutation method was applied to this GLM to test the significance of the age effects. Age values were demeaned and mean voxel values were modeled in the design matrix. Age entries were separated into two groups based on the gender of the participant so that contrasts could be used to analyze age and sex effects. The pixel-wise correlation between age and FA or MD values across subjects were investigated by testing 5000 permutations of the data. All results reported here are thresholded at $p < 0.05$ corrected for multiple comparisons using family-wise error rate (FWE) (Flitney and Jenkinson).

Additionally, we calculated average FA and MD values along each fiber tract that demonstrated significant age-associated differences in TBSS analysis. The goal was to quantify the strength of these associations in each tract. The mean values were calculated using a population-specific fiber tract atlas. This atlas was generated by tracking each pathway for each subject, transforming the pathways to the subject-template space and then averaging across subjects. We also compared the rate of these changes across tracts to investigate if the changes were global; i.e. whether all tracts followed similar trajectories of development.

Acknowledgments

This research was supported by NIH R01 HD050662 to EPD and NIH NS-41298 and HD-51852 to CAS. The authors wish to thank the families who participated in this project. The assistance of Megan Faulkner, Natalie Hernandez, Christina Canino and Susan Jackman is gratefully acknowledged. We also wish to thank Sandra Waelin, Anna Wiebel and Daniel Chang for their assistance in data processing and analysis.

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Research Highlights

- Age associated differences in brain white matter during preadolescent period.
- Development of frontal and temporal pathways demonstrated for the first time.
- Major fiber tracks show similar trajectories of development.
- Differences between sexes in brain white matter development.

Figure 1 (a)

Figure 1 (b) Parahippocampal portion of the Cingulum

Figure 1.

Major fiber tracts that showed statistically significant differences associated with age. In this figure the T1 weighted MNI152 standard brain was used as the background and each fiber tract is overlaid in green. The p-values were overlaid in red-yellow colors for FA (top row) and blue-cyan colors for MD (bottom row) (note that the thresholded statistic images were thickened using `tbss_fill` function of FSL, filling it out into the local fiber tracts for better visibility). FA increased and MD decreased significantly along major fiber pathways. (a) Both rows, left to right: Thalamic projections, IFO, ILF, SLF, cingulum, UF and CST; (b) right cingulum (parahippocampal region) shown on coronal and sagittal cross sections. Note that right cingulum in the parahippocampal region did not have a significant increase in FA but there was a significant decrease in MD. The images are presented in the radiological orientation (left side of the image corresponds to the right side of the brain).

Figure 2.

For each subject the mean FA and MD values in the seven fiber tracts shown in figure 1 were calculated and plotted against age. The linear trend lines were also included in each plot to demonstrate typical variation of DTI parameters by age.

Table 1

Descriptive Information for the Study Sample

Study Sample (<i>N</i> = 126)	
Child Age (<i>years</i>)	8.1 ^{<i>a</i>}
Sex of Child (% Male)	53
Maternal Age (<i>years</i>)	36.5 ^{<i>b</i>}
Married or Cohabiting (%)	87
Education (%)	
High school or equivalent	33
Associates or vocational	22
Bachelors degree	24
Graduate degree	14
Annual Household Income (%)	
\$0 – \$30,000	15
\$30,001 – \$60,000	22
\$60,001 – \$100,000	29
Over \$100,000	32
Race/Ethnicity (%)	
Non-Hispanic White	43
Hispanic	35
Asian	13
African American	6

^{*a*} *SD* = 1.3, range = 6 – 11

^{*b*} *SD* = 6.7, range = 24 – 52

Table 2

Average and standard deviation of FA and MD in each fiber tract across all subjects, and the percentage change per year.

	Fractional Anisotropy				Mean Diffusivity ($\times 10^{-3} \text{ mm}^2/\text{s}$)			
	Average	St.dev.	Slope per year	% increase per year *	Average	St.dev.	Slope per year	% decrease per year *
CST	0.54	0.14	0.0040	0.74 %	0.76	0.08	-0.0062	0.82 %
ATR	0.46	0.13	0.0034	0.74 %	0.81	0.16	-0.0059	0.73 %
IFO	0.44	0.15	0.0034	0.77 %	0.81	0.09	-0.0062	0.76 %
ILF	0.42	0.15	0.0033	0.79 %	0.82	0.10	-0.0074	0.90 %
SLF	0.41	0.14	0.0029	0.71 %	0.81	0.09	-0.0057	0.70 %
Cing. (CG)	0.44	0.18	0.0032	0.73 %	0.80	0.09	-0.0043	0.54 %
UNC	0.41	0.12	0.0026	0.63 %	0.82	0.17	-0.0051	0.62 %

* The percentage change per year is calculated as the ratio of the fitting slope obtained in the linear regression analysis over the mean value from all subjects ($\times 100\%$)