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Longitudinal Characterization of White Matter Maturation During Adolescence

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Abstract

Background: Late adolescence is comprised of considerable developmental transitions, though brain maturational changes during this period are subtle and difficult to quantitatively evaluate from standard brain imaging acquisitions. To date, primarily cross-sectional studies have characterized typical developmental changes during adolescence, but these processes need further description within a longitudinal framework.

Method: To assess the developmental trajectory of typical white matter development, we examined 22 healthy adolescents with serial diffusion tensor images (DTI) collected at a mean age of 17.8 years and 16-months later. Diffusion parameters fractional anisotropy, and mean, radial, and axial diffusivity were subjected to whole-brain voxelwise time point comparisons using tract-based spatial statistics.

Results: At follow-up, adolescents showed significant change (≥ 153 contiguous voxels each at $p<.01$) in diffusion properties, including in bilateral superior longitudinal fasciculi, superior corona radiata, anterior thalamic radiations, and posterior limb of the internal capsule. Overall, correlations with cognitive performances suggested behavioral improvement corresponding with white matter changes.

Conclusion: These longitudinal DTI findings support continued microstructural change in white matter during late adolescence, and suggest ongoing refinement of projection and association fibers into early adulthood.

Keywords

Diffusion tensor imaging; Adolescence; White matter; Development; Maturation

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1. Introduction

Late adolescence is comprised of extensive social, biological, and cognitive change. Despite significant developmental transitions, brain maturation during this period is comparatively subtle. Conventional MRI has typically shown a global increase in white matter volume during adolescence (Giedd et al., 1999; Giedd, 2008), with a prominence of fronto-parietal development (Benes, 1989; Huttenlocher, 1990; Yakolev and Lecours, 1967; but see also Nagel et al., 2006). Concomitant decline in cortical volume and thickness occurs during this time, likely reflecting the selective pruning of superfluous neuronal connections (Tamnes et al., 2009), while axonal myelination of neurons continues through early adulthood (Giedd, 2004; Lenroot and Giedd, 2006; Sowell et al., 2002). These combined processes refine the adolescent brain and contribute to more efficient functioning and complex behaviors (Giedd, 2008).

These findings have been expanded with the use of diffusion tensor imaging (DTI), which allows *in vivo* access to the microstructure of brain pathways through gradients that measure the rate and direction of water molecule dispersion. Two common scalar measures used to infer tissue structure are fractional anisotropy (FA), or directionally-restricted diffusion, and mean diffusivity (MD), or the overall magnitude of diffusion. FA values range from 0 for isotropic (unrestricted) diffusion to 1 for anisotropic (restricted) diffusion. Water diffuses equally in all directions in mediums without structural barriers, as in cerebrospinal fluid (Cascio et al., 2007). This is in contrast to the myelinated fibers of white matter, where diffusion is restricted and greater parallel than perpendicular to fiber tracts. Thus, high FA values indicate greater anisotropy and highly organized and myelinated bundles, but are also influenced by axon size and density, pathway geometry, and fiber intersections (Beaulieu, 2002; Mamata et al., 2002; Shimony et al., 1999).

Cross-sectional studies have documented linear increases in FA and decreases in MD across typical adolescent development continuing through the second decade of life (Barnea-Goraly et al., 2005; Bonekamp et al., 2007; Giorgio et al., 2008; Mukherjee et al., 2001; Schmithorst et al., 2002). Recent evidence suggests an exponential trend in FA increase, with the most rapid change occurring from about 5-8 years of age and plateauing by the late teens to early twenties (Lebel et al., 2008). The growth in FA is associated with a decrease in diffusion perpendicular to fiber pathways, which suggests heightened bundle density or myelination. While decreases in radial diffusivity (RD) and to a lesser extent, axial diffusivity (AD) are reported during early development (Mukherjee et al., 2002; Qiu et al., 2008; Snook et al., 2005; Suzuki et al., 2003), there is indication that AD increases may occur during adolescence (Ashtari et al., 2007). Some regions in the periphery of tracts show an increase in FA but do not exhibit corresponding increases in white matter density. This pattern may reflect ongoing strengthening of connections and increased organization and coherence (Barnea-Goraly et al., 2005).

A few cross-sectional studies and one longitudinal study have shown FA increases in young adolescents in bilateral superior longitudinal fasciculus, superior corona radiata, thalamic radiations, posterior internal capsule, corticospinal tract, arcuate fasciculus, superior and mid-temporal white matter, inferior parietal white matter, and the corpus callosum (Ashtari et al., 2007; Bonekamp et al., 2007; Giorgio et al., 2008; Giorgio et al., 2010; Tamnes et al., 2009). Cross-sectional evidence from diffusion kurtosis imaging has identified ongoing increases in FA and mean kurtosis in prefrontal areas in adolescents indicating growth in microstructural complexity (Falangola et al., 2008).

The ability to engage in complex cognitive processing in adolescence is associated with coordinated neurobiological mechanisms that include synaptic proliferation and pruning as well as axonal ensheathment (Huttenlocher, 1979). Although it is widely accepted that

myelination correlates with efficient cognitive performance (Luna and Sweeney, 2001; Paus et al., 1999; Paus et al., 2001), the correspondence between white matter maturation and cognitive improvement has only recently been characterized with specificity. DTI has provided the basis for much of this work, demonstrating, for instance, that intellectual functioning in youth is associated with the development of white matter circuitry in bilateral frontal, occipito-parietal, and occipito-temporo-parietal regions (Schmithorst et al., 2005). In addition, the reading skills of children and adolescents improve with white matter changes in the internal capsule, corona radiata, and temporo-parietal regions (Beaulieu et al., 2005; Nagy et al., 2004; Niogi and McCandliss, 2006; Qiu et al., 2008), and greater left lateralization of the arcuate fasciculus fibers is associated with improved phonological processing and receptive vocabulary (Lebel and Beaulieu, 2009). Visuospatial working memory capacity is linked to a fronto-intraparietal network (Olesen et al., 2003), while better visuospatial construction and psychomotor performance are associated with high corpus callosum FA (Fryer et al., 2008). Faster response inhibition in children is associated with higher FA and lower perpendicular diffusivity in the right inferior frontal gyrus and presupplementary motor cortex (Madsen et al., 2009).

To date, studies of microstructural white matter changes have been primarily cross-sectional and therefore results offer limited conclusions. The current study employs a longitudinal framework to characterize maturational changes in white matter during a critical adolescent juncture, representing the transition into early adulthood (ages 16-21). Using DTI, youth were examined at two time-points across a 16-month period. Based on previous findings, we expected age-related changes in white matter within frontal and frontal-parietal tracts, thalamic pathways, the internal capsule, corticospinal tracts, and corpus callosum. Specifically, we hypothesized an increase in FA and decrease in MD over time in these areas. To further explore anisotropic alterations, we examined RD and AD changes over time (Le Bihan et al., 2001). A secondary aim was to determine whether degree of white matter maturation during late adolescence would be linked to performance on measures of working memory, executive functioning, and learning and recall measured at the end of the white matter assessment interval.

2. Results

Paired samples *t*-tests, corrected with intensity and cluster-based thresholding (≥ 153 contiguous voxels with each showing the effect at $p<.01$), revealed 4 clusters in which adolescents showed significantly higher FA at Time 2 than at Time 1. FA increased over time in the right hemisphere in: the superior longitudinal fasciculus (SLF), superior corona radiata (SCR), anterior thalamic radiations, and posterior limb of the internal capsule (PLIC) ($p<.005$, see Figure 1); no FA decreases were observed. Seven clusters were identified showing a decrease in MD from Time 1 to Time 2: left and right SLF, left and right SCR, left PLIC, anterior portions of the left inferior fronto-occipital fasciculus (IFOF), and left cerebellar fibers ($p<.005$); one unexpected area of increased MD was noted in the right posterior IFOF. Examination of RD revealed decreased perpendicular diffusion in six clusters, three of which were located in regions that also showed increased FA, namely the right SLF, anterior thalamic radiations, and PLIC ($p<.001$) (see Figure 2). Additional tracts showing decreasing RD were found in the left hemisphere including the SLF, SCR, and anterior thalamic radiations ($p<.001$); no increases in RD were observed. Changes in AD over time were detected in three clusters: an increase in the right posterior IFOF, and unexpected decreases in the left anterior IFOF and left cerebellar fibers ($p<.005$). These anatomical changes are presented in Table 1.

To evaluate the potential influence of age at study enrollment and duration of interscan interval, hierarchical regression analyses were performed entering these variables as covariates in the first step ($N = 22$). Changes in FA, MD, RD, and AD were consistent with those reported above

after controlling for these variables. One exception was noted in RD of the left SCR, which only reached marginal significance (p = .08) in this hierarchical regression analysis.

Due to the disparate number of males and females in our sample, the evaluation of potential gender dimorphisms was limited. Exploratory analyses indicated that males showed similar changes over time (large effect sizes) in all clusters reported for the full sample. Females showed medium effects sizes in FA clusters, but demonstrated similar patterns of change in MD, RD, and AD to males.

To better understand how developmental changes in anisotropy and diffusivity relate to cognitive outcome, exploratory analyses (N=22) examined relationships between change in diffusion indices over time and neurocognitive performance at Time 2. In the right hemisphere, greater increase in FA and decrease in RD in the PLIC were associated with higher performance on WAIS-III Digit Span Backward (FA: r=.43, p=.04; RD: r=−.44, p=.04) and D-KEFS Letter Fluency (FA: r=.44, p =.04; RD: r=−.51, p=.01), as predicted. In the right IFOF, unexpected increased MD yet anticipated increased AD were linked to better performances on WASI Block Design (MD: r=.53, p=.01; AD: r=.51, p=.02), CVLT-II Trial 1 (MD: r=.46, p=.03; AD: r=.47, p=.03), and CVLT-II Short Delay Free Recall (AD: r=.44, p=.04). Within the left hemisphere, greater decrease of MD in the PLIC was associated with poorer performance on WMS-III Logical Memory Recall (r=.46, p=.03) and Recognition (r=.56, p=.007). Greater decrease in RD in the left anterior thalamic radiations was also associated with poorer performance on WMS-III Logical Memory Recognition (r=.45, p=.03). Regarding the latter two findings, younger age at Time 2 was associated with greater decreases in MD in the left PLIC (r=.−.46, p=.03) and in RD in the left anterior thalamic radiations (r=.−.45, p=.04).

3. Discussion

The current study provides a longitudinal characterization of microstructural white matter maturation during late adolescence. We found significant changes in anisotropy and diffusivity that reflect widespread alterations in fiber pathways during this developmental period. Our findings are consistent with previous cross-sectional studies that show increased anisotropy in the SLF, corona radiata, thalamic fibers, internal capsule, and IFOF with age (Barnea-Goraly et al., 2005; Giorgio et al., 2008; Giorgio et al., 2010; Schmithorst et al., 2002) and suggest continued organization of these brain regions.

While many association fibers including the SLF and IFOF appear to reach near maximal anisotropic change between 13 and 20 years of age, projection fibers comprising the PLIC approach an asymptotic point between the ages of 21 and 24 (Lebel et al., 2008). Commensurate with our findings, this region showed significant anisotropic increase and perpendicular diffusivity decrease, confirming recent data demonstrating longitudinal FA increases in the PLIC (Giorgio et al., 2010). Importantly, our findings are in agreement with white matter density increases in this region during adolescence (Paus et al., 1999; Schmithorst et al., 2002) and provide clarification to previous speculation that anisotropic alterations in this structure may occur during the period between early adolescence and adulthood (Snook et al., 2005). Moreover, our results suggest that maturation of the PLIC is associated with the refinement of skills in complex attention and phonemic fluency. Ascending and descending tracts projecting through the PLIC include the corticospinal tract, corticobulbar fibers, and thalamocortical somatosensory radiations (Kretschmann, 1988; Paus et al., 1999), and may contribute to the component processes involved in these cognitive functions (Gauthier et al., 2009; Hamilton et al., 2008; Royall et al., 2002).

Although we expected age-related anisotropic increases in the frontal regions and corpus callosum, our results resemble recent findings showing prominent changes in subcortical

projection/association fibers and deep gray matter fibers, with less change in major compact white matter tracts during adolescence (Lebel et al., 2008). One area of significant anisotropic increase within deep gray matter was noted in the anterior thalamic radiations, suggesting that the relay between the cortex and thalamus may be undergoing a refinement of connections in response to continued environmental input. Considering that the thalamus shows a substantial percent increase in FA and decrease in MD (Lebel et al., 2008; Snook et al., 2005; Zhang et al., 2005) and that white matter density in inter-thalamic pathways increases from childhood to adolescence (Barnea-Goraly et al., 2005), ongoing myelination and wiring are likely contributors to anisotropic change in this region during late adolescence. Although reduced RD in the left hemisphere thalamic radiations was associated with poorer verbal memory recognition, age may be a contributing factor, as younger participants demonstrated greater RD reduction in this region over time. Maturation of these pathways may be more closely related to enhancements in behavioral modulation and sensorimotor coordination in youth, which were not directly assessed here.

Evidence for bilateral white matter changes in the SLF, SCR, thalamic fibers, and PLIC were found in the examination of MD and RD, indices that appear to have greater sensitivity to maturational alterations (Eluvathingal et al., 2007; Schmithorst et al., 2002; Schneider et al., 2004). Indeed, several structures showed a significant decrease in MD, including structures that did not show significant FA change with age. This trend, also reported elsewhere (Schmithorst et al., 2002; Snook et al., 2005), suggests that MD changes may occur later than anisotropic increases (Lebel et al., 2008). An additional consideration is that the quantification of FA in regions of complex fiber architecture is difficult and can interfere with the detection of true anisotropic changes. In contrast, estimates of MD, which are generally more robust, may be more sensitive to changes in diffusivity (Schmithorst et al., 2002).

Analysis of AD and RD indicated that developmental increases in FA may be primarily associated with a decrease in perpendicular diffusion, a pattern that has been attributed to increased myelination, axonal density, and fiber compactness (Giorgio et al., 2008; Snook et al., 2005). Changes in parallel diffusion were less consistent. Two regions in our study showed decreased AD over development (left anterior IFOF and cerebellar fibers), which is a pattern supported by previous reports (Eluvathingal et al., 2007; Lebel et al., 2008; Suzuki et al., 2003). Findings from those studies, however, indicate that the decrease in RD was more pronounced than the decrease in AD, which was not evident in our results. Significantly decreased AD in the anterior IFOF and cerebellar fibers may be the result of developing axonal collaterals (Hua and Smith, 2004) and could contribute to the reduction in MD and AD observed here. Although two previous reports (Ashtari et al., 2007; Giorgio et al., 2010) document increased FA and AD with no changes in RD in adolescence, technical and demographic differences may contribute to discrepancy with current findings. Specifically, although longitudinal changes in the corona radiata, thalamic radiations, and PLIC were common between our study and that of Giorgio and colleagues (2010), we speculate that our higher proportion of males, briefer interscan interval, narrower age range, and imaging parameters (e.g., 3T field strength) may account for some divergent findings. The broader age range of samples in the former studies may capture more expansive developmental changes, whereas our findings characterize changes during a circumscribed period in adolescence. This is apparent when comparing the magnitude of change in FA, which was largest in the anterior thalamic radiations and SCR in our study, but was more prominent in the cerebral peduncle and posterior corona radiata in Giorgio and colleagues (2010). These differences underscore the dynamic nature of ongoing changes that characterize adolescent and young adult development.

Gender differences in white matter development have been reported in the frontal association fibers, parietal and occipito-parietal areas, the arcuate fasciculus, and corpus callosum

(Schmithorst et al., 2008; Schneiderman et al., 2007), whereas others report few or no differences (Eluvathingal et al., 2007; Giorgio et al., 2008; Hasan et al., 2007; Lebel et al., 2008; Muetzel et al., 2008). In the current study, changes in anisotropy that reflect maturation of the right SLF and PLIC showed smaller effect sizes in females and may coincide with previous findings of increased volumetric growth of white matter in male than female adolescents (De Bellis et al., 2001; Lenroot et al., 2007; Perrin et al., 2009). Nonetheless, interpretation is limited being that our sample was small and not equally distributed across genders.

Cognitive correlates of anisotropic and diffusional change over time were generally consistent with expectations, with increased FA and AD contributing to higher performances in the areas of complex attention and working memory and verbal fluency. Although significant increase in MD over time in the right IFOF were associated with improved visuoconstruction ability and learning and recall, concomitant increase in AD in this region were also associated with higher performance on these measures, suggesting that changes in AD may primarily underlie the increase in MD observed over time. The relationships between decreasing MD and RD in the left PLIC and anterior thalamic radiations, respectively, and poorer performance on aspects of contextual learning and memory may be related to age, as younger participants exhibited greater diffusivity decreases in these regions.

Despite a fairly limited sample size, this study demonstrated significant maturational changes in diffusion properties with development. These preliminary results offer a longitudinal demonstration of protracted white matter development in late adolescence, and specifically, a characterization of the complex microstructural processes in projection and association fibers that occur during this critical developmental juncture. Correlation with cognitive data suggest corresponding behavioral changes associated with white matter maturation, that are generally consistent with the notion of increased efficiency of cognitive skills with white matter development. These data, together with previous studies, provide a basis for understanding genetic and environmental influences on developmental pathways in vulnerable youth.

4. Experimental Procedure

4.1 Participants

Twenty-two typically developing adolescents (15 males and 7 females; Time 1 mean age 17.8 ± 1.4 years, range 16.2-20.6) were recruited from local high schools as part of an adolescent brain imaging project (Tapert et al., 2007). Participants and their parents or legal guardians were screened with separate, private interviews to ascertain eligibility. Exclusionary criteria were: parental history of bipolar I or psychotic disorder; complicated or premature birth (<33 weeks gestation); evidence of maternal drinking or illicit drug use during pregnancy; left handedness; history of neurological disorder or head trauma with loss of consciousness >2 minutes, learning disability or mental retardation, serious medical illness, DSM-IV Axis I disorder including any substance use disorder, nicotine dependence (Fagerstrom Test for Nicotine Dependence (FTND) score ≥ 3) (Heatherton et al., 1991), or use of psychoactive medications; MRI contraindications; and clinically abnormal brain anatomy as determined by neuroradiologist review.

Participants were from a representative range of sociocultural backgrounds (ethnicity: Caucasian 63%, Hispanic 5%, African-American 5%, Asian 9%, and multi-racial 18%; mean Hollingshead socioeconomic status: 29.3 ± 15.7, range 11-63 (Hollingshead, 1965)). At baseline, estimated IQ and academic reading achievement fell in the average to high average range. Measures of emotional functioning and psychopathological syndromes were well within normal limits, and lifetime substance use was very limited.

Participants received behavioral and neuropsychological measures and underwent a neuroimaging study after enrollment (Time 1) and at follow-up (Time 2). Follow-ups occurred 1.3 ± 0.25 years after the first imaging session (Time 2 mean age 19.2 ± 1.4 years, range 17.4-21.5). Participants showed no significant differences on the Hollingshead, emotional functioning, or psychopathological syndromes measures from baseline to follow-up. At enrollment and again at follow-up, for anyone under age 18, informed assent and consent were obtained from participants and legal guardians, respectively, and for those age 18 or older, informed consent was obtained from the participant, and separately from the parent/guardian for their participation in completing an interview on youth history and behaviors. Consent and assent procedures were in accordance with UCSD Human Research Protections Program guidelines.

4.2 Behavioral and Neuropsychological Measures

The Beck Depression Inventory (BDI) (Beck, 1978) and Spielberger State Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) assessed mood prior to scanning. The age-appropriate behavioral measure (e.g., Child Behavior Checklist (CBCL), Youth Self-Report (YSR), or Adult Self-Report (ASR)) (Achenbach and Rescorla, 2001) was completed to assay internalizing and externalizing psychopathological syndromes. The Customary Drinking and Drug Use Record (Brown et al., 1998) collected from the adolescent detailed information on quantity and frequency of lifetime and past 3-month alcohol, nicotine, and other drug use and abuse/dependence criteria. History of psychiatric and substance use disorders in biological parents was assessed by parent interview using the Family History Assessment Module (FHAM; (Rice et al., 1995).

The Wide Range Achievement Test – 3 (WRAT-3) Reading subtest (Wilkinson, 1993), Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest (Wechsler, 1999), and Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Letter scaled score (Delis et al., 2001) provided estimates of reading and language functioning and were examined in correlation analyses. Measures of neurocognitive functioning with working memory, executive functioning, or memory demands that may be linked to white matter integrity and development (Nagy et al., 2004; Olesen et al., 2003; Zahr et al., 2009) were also administered and examined in correlation analyses: Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Span backward score and Digit Span total scaled score (Wechsler, 1997b); Paced Auditory Serial Addition Test (PASAT) 3-second trial total score (Gronwall, 1974); D-KEFS Trail Making Test Switching and Verbal Fluency Category Switching scaled scores (Delis et al., 2001); WASI Block Design *T*-score; California Verbal Learning Test-II (CVLT-II) List A Trial 1, Trials 1-5, and immediate and delayed recall standard scores (Delis et al., 2000); and Wechsler Memory Scale-Third Edition (WMS-III) Logical Memory recall total score and recognition total score (Wechsler, 1997a).

4.3 MR Acquisition

Participants were imaged in a 3T General Electric Excite MR system with an 8-channel phase-array head coil (General Electric Medical System, Milwaukee, WI, USA). A scout scan ensured good head placement and whole-brain coverage. Diffusion-weighted images were collected along 15 noncollinear directions determined by the electrostatic repulsion model, which minimizes bias in measurements by sampling with approximately uniform distribution on a sphere (Jones et al., 1999), in addition to a reference image with no diffusion weighting (b=0). The diffusion encoding scheme consisted of a single-shot dual spin echo excitation optimized for minimum TE and reduction of eddy current artifacts (Reese et al., 2003). The following sequence parameters were applied and averaged over four volumes: TE/TR=93/12,000 ms, FOV=240 mm, matrix =128×128, 36 contiguous slices, 3 mm slice thickness, b-value=2000 s/mm^2. Two field maps were collected for unwarping (TE/TR=3.8/1,000 ms) to correct for

signal loss and geometric distortion due to B0 field inhomogeneities (Andersson and Skare, 2002; Jezzard and Balaban, 1995).

4.4 Data Processing

Datasets were preprocessed and subjected to tensor decomposition, as in our recent studies (Bava et al., 2009; Jacobus et al., 2009; McQueeny et al., 2009). This included corrections for head motion, eddy current distortion, and signal loss using FSL tools (FMRIB Software Library, Oxford, United Kingdom; Smith et al., 2004). Scalar diffusion indices, FA, MD, RD, and AD, were computed in native coordinate space using Analysis of Functional NeuroImages' (AFNI; Cox, 1996) diffusion plug-in routine, *3dDWItoDT* (Cox and Glen, 2006), and were examined with *Tract-Based Spatial Statistics* (TBSS; Smith et al., 2006).

TBSS analyses involved the following steps: To achieve initial alignment, FA maps were registered to an averaged FA template (FMRIB-58) in MNI-152 standard space using an affine-only registration. This was followed by a non-linear transformation into 1-mm cubic voxel dimensions (*FNIRT-FMRIB*'s Non-linear Registration Tool). Data were examined for laterality, orientation, and cross-subject anatomical alignment. Next, transformed images were averaged across subjects to create a mean diffusion image (FA), from which a white matter skeleton was derived, representing tracts common to all subjects. Individual transformed FA images were then projected onto the skeleton. To minimize partial-volume effects and areas of high inter-subject variability, values were thresholded at FA>0.2. FA values from individuals' nearest relevant tract center were assigned to the skeleton via a perpendicular search for the maximum FA value within the local skeleton structure. This process accounts for residual misalignments between subjects after the initial registration, and minimizes systematic differences in tract location between groups of subjects. MD, RD, and AD data were processed using the same nonlinear transformation, skeleton, and skeleton-projection vectors derived from the FA analysis (Smith et al., 2007). Data from each point on the skeleton formed the basis of voxelwise statistical comparisons.

4.5 Statistical Analysis

Voxelwise statistics on skeleton space FA, MD, RD, and AD data were carried out in AFNI using paired samples *t*-tests. Correction for multiple comparisons was achieved through a combination of individual voxel probability and cluster size thresholding using Monte Carlo simulation (Ward, 2000) for Type I error control. Considering that skeletonized datasets typically have an intrinsic smoothness on the order of 4 mm full width half maximum (Smith et al., 2006), this parameter was included in the multiple comparison correction. Under these criteria, only clusters ≥ 153 μl (i.e., 153 contiguous 1×1×1 voxels) with an individual voxel probability threshold of $p<0.01$, yielding a brain-wise $p<0.05$ of finding such a cluster under the null hypothesis, were interpreted. Cohen's *d* effect sizes (Cohen, 1988) were computed from the average *t*-value within each significant cluster. Due to the correlated nature of the longitudinal design, average *t*-values were computed from independent samples *t*-tests to avoid overestimation of effect size (Dunlop et al., 1996). To determine whether age at study enrollment and interscan interval accounted for significant variance in time point comparisons, hierarchical regression analyses were conducted to control for these potential confounds. Anatomical identification of tract structures was confirmed using white matter atlases (Mori et al., 2008; Wakana et al., 2004).

Exploratory analysis examined gender differences in mean FA, MD, RD, and AD in clusters showing significant time effects ($\alpha = .05$). In addition, for clusters showing significant time effects, change scores computed for each diffusion index (Time 2 - Time 1) were correlated using Pearson's *r* with Time 2 measures of neurocognitive functioning ($\alpha = .05$).

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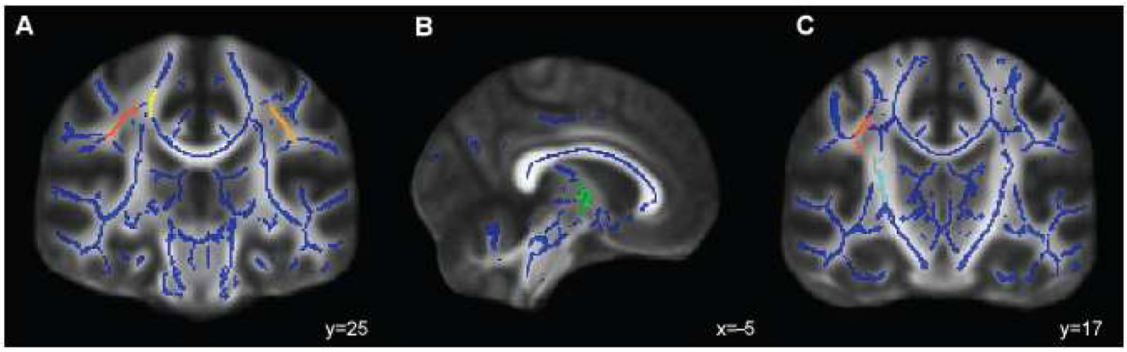

Figure 1.

Clusters of significant change (≥ 153 μl, $p<0.01$) in the: (A) superior longitudinal fasciculus (right = red; left = orange), and superior corona radiata (yellow); (B) right thalamic fibers (green); and (C) right posterior limb of the internal capsule (cyan) and superior longitudinal fasciculus (red) from Time 1 to Time 2 in adolescents (N=22). Results are superimposed on the fiber skeleton (blue) and overlaid on a standardized FA template. Images are in radiological convention.

Figure 2.

Overlapping regions of significant change in fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) from Time 1 to Time 2 among adolescents (*N*=22). Increased FA in the thalamic radiations, superior longitudinal fasciculus and posterior limb of the internal capsule was associated with an equal or greater decrease in RD over time.

Abbreviations. ATR = Anterior thalamic radiations; SLF = Superior longitudinal fasciculus; PLIC = Posterior limb of internal capsule; SCR = Superior corona radiata; IFOF = Inferior fronto-occipital fasciculus; CF = Cerebellar fibers; R = Right; L = Left.

Table 1

Regions showing significant change (153 μl, $p<.01$) from Time 1 to Time 2 in fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) in typically developing adolescents ($N=22$).

Anatomic region	Cluster Size (voxels)	MNI Coordinate* x	y	z	Effect Size (Cohen's *d*)†	Mean Difference (Time 2 – Time 1)
FA						
Anterior thalamic radiations R	507	−8.1	9.2	7.3	1.05	.04
Superior longitudinal fasciculus R	327	−31.2	22.8	39.1	.92	.05
Posterior limb of internal capsule R	223	−26.5	17.1	13.6	.87	.03
Superior corona radiata R	157	−21.4	27.7	46	.95	.05
MD						
Posterior limb of internal capsule L	751	23	15.5	7.4	−1.24	−.04
Superior corona radiata L	525	19	21.9	48.9	−1.17	−.03
Superior longitudinal fasciculus L	354	34.7	29	35.4	−1.15	−.03
Inferior (anterior) fronto-occipital fasciculus L	261	13.5	−53.7	16.9	−1.50	−.07
Superior longitudinal fasciculus R	210	−32.4	23.1	37.8	−1.02	−.03
Cerebellar fibers L	186	26.6	55.9	−28.7	−1.23	−.05
Superior corona radiata R	172	−19.1	28.6	50.5	−.94	−.03
Inferior (posterior) fronto-occipital fasciculus R	300	−11.5	83.8	26.6	1.14	.10
RD						
Superior longitudinal fasciculus R	486	−33.4	22	36	−1.07	−.05
Posterior limb of internal capsule R	319	−25.7	15.4	13.7	−.90	−.05
Superior longitudinal fasciculus L	273	34	26.4	35.9	−1.24	−.04
Anterior thalamic radiations R	264	−7	6.6	6.3	−1.30	−.05
Anterior thalamic radiations L	215	6.5	8.7	9.7	−1.58	−.06
Superior corona radiata L	155	12.7	−54.1	18.5	−1.35	−.07
AD						
Inferior (posterior) fronto-occipital fasciculus R	266	−8.8	85.4	24.1	1.07	.20
Inferior (anterior) fronto-occipital fasciculus L	203	12.6	−54.2	18.4	−1.69	−.11
Cerebellar fibers L	170	26.8	55.4	−28.9	−1.39	−.07

L=Left; R=Right

* Coordinates of the center of mass in significant clusters

† Effect size from the average *t*-value for each cluster