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White Matter Development in Adolescence: Diffusion Tensor Imaging and Meta-Analytic Results

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Background: **In light of the evidence for brain white matter (WM) abnormalities in schizophrenia, study of normal WM maturation in adolescence may provide critical insights relevant to the neurodevelopment of the disorder. Voxel-wise diffusion tensor imaging (DTI) studies have consistently demonstrated increases in fractional anisotropy (FA), a putative measure of WM integrity, from childhood into adolescence. However, the WM tracts that show FA increases have been variable across studies. Here, we aimed to assess which WM tracts show the most pronounced changes across adolescence.** ***Methods:*** **DTI was performed in 78 healthy subjects aged 8–21 years, and voxel-wise analysis conducted using tract-based spatial statistics (TBSS). In addition, we performed the first meta-analysis of TBSS studies on WM development in adolescence.** ***Results:*** **In our sample, we observed bilateral increases in FA with age, which were most significant in the left superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and anterior thalamic radiation. These findings were confirmed by the meta-analysis, and FA increase in the bilateral SLF was the most consistent finding across studies. Moreover, in our sample, FA of the bilateral SLF showed a positive association with verbal working memory performance and partially mediated increases in verbal fluency as a function of increasing age.** ***Conclusions:*** **These data highlight increasing connectivity in the SLF during adolescence. In light of evidence for compromised SLF integrity in high-risk and first-episode patients, these data suggest that abnormal maturation of the SLF during adolescence may be a key target in the neurodevelopment of schizophrenia.**

Key words: adolescence/development/diffusion tensor imaging/superior longitudinal fasciculus/verbal fluency/working memory

Introduction

Schizophrenia is considered a neurodevelopmental disorder,[1] and abnormal trajectories of brain development in adolescence have been associated with the typical onset of psychosis in late adolescence.[2] Therefore, study of normal brain maturation across adolescence may provide critical insights into the developmental processes involved in the disorder. Considering the strong evidence for brain white matter (WM) abnormalities in schizophrenia,[3,4] study of normal adolescent WM development is highly relevant. In particular diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) measure sensitive to microstructural WM changes[5] has demonstrated WM abnormalities in first-episode and medication-naïve patients and patients at clinical high risk for psychosis, suggesting a primary role for WM abnormalities in the disease process.[4] Moreover, microstructural integrity of specific WM tracts is found to be associated with severity of positive symptoms, negative symptoms, or neurocognitive dysfunction in first-episode and recent-onset patients and predictive of psychosis and functional outcome in individuals at high risk for psychosis.[4] For example, reduced integrity of the superior longitudinal fasciculus (SLF) correlated with poorer verbal working memory performance in recent-onset patients.[6] In adolescents at high risk for psychosis, microstructural integrity

of the inferior longitudinal fasciculus (ILF) predicted social and role functioning at 15-month follow-up, and interestingly, failed to show the same age-related changes as observed in healthy controls.[7]

Early structural MRI studies have demonstrated global increases in WM volume across the lobes[8] and specific increases in WM density of the corticospinal tract and SLF from childhood into adolescence.[9] DTI has demonstrated significant increases in fractional anisotropy (FA) from childhood into adolescence and early adulthood,[10,11] suggestive of increasing myelination, fiber packing density, axon diameter, or fiber coherence.[5] Voxel-based analyses (VBA) identified FA increases in several WM areas, including the posterior limbs of the internal capsule (PLIC), left SLF, right cingulum, posterior corpus callosum (CC), and left prefrontal WM.[10,11]

While VBA has the advantage of unbiased, automated whole brain analysis, limitations include partial volume effects and misregistration errors. Tract-based spatial statistics (TBSS), a variant of VBA designed for DTI data,[12] minimizes these limitations. Several TBSS studies have confirmed increases in FA from childhood into adolescence and early adulthood.[13–17] However, while specific tracts were identified in different studies, clear findings are not evident. One study found significant FA increases in the body of the CC and right superior corona radiata (sCR),[13] while another study did not observe FA increases in the CC but found increases in the right sCR, right PLIC, right SLF, and right anterior thalamic radiation (ATR).[14] Other studies identified more widespread FA changes, which included the left SLF,[15,16] anterior limbs of the internal capsule (ALIC),[17] bilateral ILF/inferior fronto-occipital fasciculus (IFOF),[15] and right cingulum.[16] These data suggest that FA increases are notable across adolescent development, but variable results limit the specificity, and thus interpretation of these findings.

Therefore, in the present study, we aimed to determine which WM tracts, as measured with TBSS, show the most consistent change across adolescence. For this purpose, we first assessed a cohort of 8- to 21-year-old healthy subjects using DTI and examined age-related FA changes with TBSS. Next, we conducted the first meta-analysis of TBSS studies on healthy adolescent WM development to assess our results in the context of the larger sample sizes available with meta-analysis. As normal development is associated with changes in frontal lobe functioning,[18] we hypothesized that WM tracts connecting the frontal lobe with other cortical and subcortical regions would exhibit the most pronounced FA increases. In addition, we evaluated the relationship between neurocognitive performance and the WM tracts that were identified in both our sample and the meta-analysis, to provide data on the functional consequences of WM tract development. Finally, we discuss our results in the context of DTI findings in schizophrenia, to examine the extent to which WM regions that actively develop during adolescence may also be implicated in the early stages of the disorder.

Methods

Zucker Hillside DTI-TBSS Analysis in Healthy Children

Participants. Seventy-eight healthy individuals (53% females) between the ages of 8 and 21 years (mean 15.3±3.7) were recruited through local advertisements and by word of mouth. Age distribution was as follows: 8–12 years, $n = 16$ (21%); 13–17 years, $n = 33$ (42%); and 18–21 years, $n = 29$ (37%). Written informed consent was obtained from participants or if the participant was a minor, from a parent or guardian; all minors provided assent. Participants had no current or past history of a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* axis I psychiatric disorder as assessed by structured or semistructured diagnostic interview. Other exclusion criteria included: (1) intellectual disability, (2) learning disability, (3) medications with known adverse cognitive effects, (4) MRI contraindications, (5) pregnancy, and (6) significant medical illness that could affect brain structure. Mean full scale IQ was 106±12, as measured using the Wechsler Abbreviated Scale of Intelligence (WASI) for 60 subjects and estimated from the Wide Range Achievement Test (WRAT-3) for 12 subjects (data missing for 6 subjects). Handedness was determined using the Edinburgh Handedness Inventory, and median laterality quotient was 0.88 (range −1 to 1; data missing for 8 subjects). Subjects were administered a battery of neurocognitive tests designed to assess attention, executive functions, language ability, visuospatial processing, sensorimotor functions, memory and learning. This study was approved by the Institutional Review Board of the North Shore—Long Island Jewish Health System.

DTI Acquisition. MRI exams were conducted at North Shore University Hospital, Manhasset, NY, on a 3T GE scanner (GE Signa HDx; General Electric, Milwaukee, WI). DTI data were acquired using single shot echo planner imaging, and a double spin echo to decrease distortions due to eddy currents, with the following parameters: repetition time = 14000 ms, echo time = minimum, matrix = 128 × 128, field of view = 240 mm, slice thickness = 2.5 mm, and 51 contiguous axial slices aligned to the anterior and posterior commissures. A total of 36 DTI volumes were obtained for each subject that included 31 volumes with diffusion gradients applied along 31 noncollinear directions ($b = 1000$ s/mm^2) and 5 volumes without diffusion weighting.

DTI Processing and Analysis. All scans were reviewed by a radiologist to ensure that no gross abnormalities

were evident. All images were visually inspected and four subjects were excluded due to significant motion artifacts. DTI data were processed and analyzed using the FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk/fsl/, accessed March 23, 2012). Head motion and eddy current induced distortions were corrected through affine registration of the diffusion-weighted images to the first B0 image. The gradient directions were corrected according to the rotation parameters. Next, nonbrain tissue was removed using the Brain Extraction Tool. The DTIFIT tool was then used to fit a diffusion tensor model to the raw diffusion data at each voxel, fitting the model with weighted least squares.

Voxel-wise statistical analysis of the FA data was carried out using TBSS in FSL.[12] First, all subjects' FA data were aligned into a common space through nonlinear registration to a target image. Because of the age range of our subjects, registration was done by aligning every FA image to every other one, to identify the ''most representative'' subject, and using this as the target image. The target image was then affine aligned into MNI152 standard space, and every image was transformed into 1 × 1 × 1 mm MNI152 space by combining the obtained linear and nonlinear transformation parameters. Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. The FA threshold for the mean FA skeleton was set at 0.2. Each subject's aligned FA data were then projected onto this skeleton, and the resulting data were fed into voxel-wise cross-subject statistics. To test for local correlations between age and FA, permutation-based testing was done, and inference on the statistical maps carried out using threshold-free cluster enhancement.[19] The null distribution was built up over 5000 random permutations across the image. The clusters were then thresholded at a level of $P < .05$, which is fully corrected for multiple comparisons (ie, family-wise error). Anatomical localization of significant WM clusters was determined with the probabilistic cortical, subcortical, and WM tractography atlases provided in FSL and an MRI atlas of human WM anatomy.[20]

Meta-Analysis of DTI-TBSS Studies in Healthy Children

A literature search was performed in PubMed (National Library of Medicine; www.pubmed.com, accessed March 23, 2012) using the terms ''DTI'' AND (Adolescence OR Development*). Articles that met inclusion criteria were cross-referenced to identify additional studies. Inclusion criteria were: (1) application of DTI to assess age-related WM changes in healthy subjects, (2) mean age of subjects between 12 and 18 years or inclusion of a child group (mean age < 12 years) and a young adult group (mean age > 18 years) for group comparison, (3) analysis of DTI images with TBSS, and (4) direct analyses of age-FA relationships, either through correlation or group comparison. Studies that conducted only age-FA correlations in WM areas that had first demonstrated a relationship between FA and a cognitive measure were not included. WM FA was the primary DTI measure of interest. Only TBSS results that were corrected for multiple comparisons or used a cluster-size threshold were included for meta-analysis.

The Effect-Size version of the Signed Differential Mapping (ES-SDM) software was used (www.SDMproject.com, accessed March 23, 2012).[21,22] In ES-SDM, statistical maps of imaging data can be used, and when not available, they can be combined with peak coordinates. Interestingly, the inclusion of statistical maps allows efficient voxel-based meta-analyses with a much smaller number of studies than in standard coordinate–based meta-analyses.[21] If a statistical map is available, the conversion to unbiased effect size and variance maps is straightforward using standard formulas.[23] For peak coordinates, ES-SDM implements a novel approach that recreates the effect-size and variance maps by applying a 20 mm full-width at half maximum kernel to the peak coordinates. The procedure is detailed elsewhere.[21]

For the aim of this study, we adapted the ES-SDM software to allow meta-analyses of TBSS studies by creating a new meta-analytic template and a specific preprocessing algorithm for TBSS studies. The template was created by converting the FMRIB58 FA skeleton included in FSL to Talairach space. The new preprocessing algorithm for TBSS *t* statistic maps consisted of replacing the direct conversion of *t* statistic images to effect-size maps by the following 2-step procedure: (1) retrieval of a mass number (eg, 5000) of low-thresholded local peaks from the statistical maps, (2) incorporation of these peaks to the SDM peak-based preprocessing procedure to reconstruct the effect-size maps. With this indirect approach, all recreated effect-size maps correctly overlapped with the TBSS template, while this was not the case when in preliminary analyses we had directly used the *t* statistic images. T statistic images of included studies were provided by the primary authors, and we were able to apply this approach for 3 studies,[13,14,17] and our own data, while for the other 3 studies we used the peak coordinates.[15,16]

The meta-analysis combined the data from each study, ie, calculating a weighted mean of all the studies. In SDM, random-effects models are implemented in which studies with larger sample size or lower variability contribute more, and effects are assumed to randomly vary between samples. The statistical significance is assessed with a voxel-based permutation test. Based on the empirical validation of ES-SDM,[21] we used an uncorrected $P = .005$ as the main threshold. To further reduce the possibility of false-positive results, we used an additional peak-height threshold of $Z > 1$ and extent threshold of 10 voxels. Furthermore, to assess the robustness of

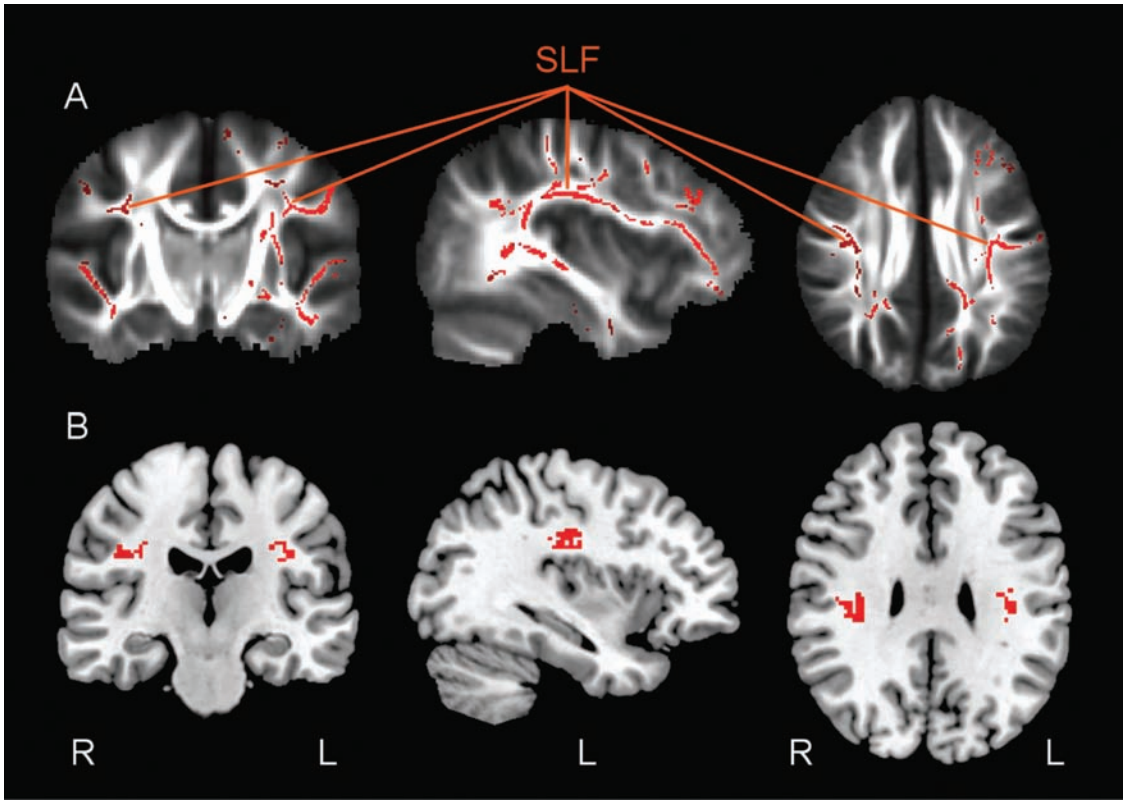

Fig. 1. Panel A: Age-related increases in fractional anisotropy (FA) in 78 healthy subjects 8–21 years old ($x = -36$, $y = -16$, $z = 31$). Significant clusters (red) are overlaid on the mean FA image of all subjects ($P < .05$, corrected). Panel B: Age-related increases in FA of the bilateral superior longitudinal fasciculus (SLF) in a meta-analysis of studies on healthy adolescent white matter development ($x = -36$, $y = -19$, $z = 30$). Significant clusters (red) are overlaid on an MRIcron template (www.mricro.com/mricron) for display purposes ($P < .005$, $Z > 1$, > 10 voxels).

findings, sensitivity analyses (repeating the meta-analysis leaving one study out each time) were conducted.

Neurocognitive Correlates of Healthy DTI Changes

Tracts that showed significant age-associated increases in FA in both our sample and the meta-analysis, were then investigated in relationship to neurocognitive function in our sample. We selected appropriate neurocognitive tests based on reports from the literature relating specific test performance to implicated tracts. Tracts were segmented using probabilistic tractography in each subject's native space.[24] Seed regions, way points, and target regions were drawn on FSL's MNI152 T1 and FMRIB58 FA templates and then transferred to subjects' native space, using the parameters obtained through affine registration of the b0 images to the MNI152 T1 template. After tractography, each tract was thresholded at a normalized probability value, and mean FA of each tract was extracted.

The relationships between FA and test performance were analyzed using linear regression. Because FA and neurocognitive performance are both known to improve with age and an association between them could merely arise from their association with age, we also tested whether age-related FA changes mediate age-related changes in test performance using a mediation model.[25] Hierarchical linear regression was performed with age first entered as predictor of test performance and then FA added as a second predictor. FA was considered to be a partial mediator of test performance when (1) FA was a significant predictor of test performance after adjusting for age, and (2) FA partially explained an observed age effect, ie, an association between age and test performance was attenuated when FA was entered into the model. Raw scores of test performances were used.

Statistical tests were conducted in the Statistical Package for the Social Sciences (SPSS), version 11.5.1 (IBM; www.spss.com, accessed March 23, 2012).

Results

Zucker Hillside Analysis

Overall, significant increases in FA with age were observed bilaterally in deep and superficial WM ($P <$ .05, corrected; see figure 1A and table 1). In the left hemisphere, a cluster of 13 154 voxels included frontal, parietal, temporal, and occipital WM and association, projection, and interhemispheric pathways. In the right

Table 1. White Matter Clusters Showing a Positive Correlation Between Age and Fractional Anisotropy in 78 Healthy Subjects (8–21 Years).

Cluster	Peak-Coordinate (MNI *x*, *y*, *z*)	Cluster Size (voxels)	Hemisphere; Lobe	WM Tract
1	−43, −5, −15	13 154	Left; Frontal, Temporal, Parietal, Occipital	ATR/ALIC, CC genu and splenium, CR posterior and superior, CST, EC, F-minor, IFOF, ILF, PLIC, PTR/OR/F-major, SLF (frontal and parietal), Tapetum, UF
2	38, −44, 5	2842	Right; Parietal, Temporal, Occipital	CC splenium, CR posterior, CST, IC retrolenticular, IFOF and ILF (occipito-temporal), PTR/OR, SLF (temporal)
3	37, −14, 30	861	Right; Parietal, Frontal	SLF (fronto-parietal)
4	−31, −11, −26	345	Left; Temporal	(Parahippocampal WM, anterior; Hippocampal WM)
5	43, −22, 38	234	Right; Parietal	(Postcentral gyrus WM)
6	30, −14, 25	109	Right; Parietal	CR superior, EC, SLF
7	−40, 7, −35	20	Left; Temporal	Temporal pole
8	−39, 6, −26	4	Left; Temporal	UF

Note: ALIC, anterior limb of internal capsule; ATR, anterior thalamic radiation; CC, corpus callosum; CR, corona radiata; CST, cortico-spinal tract; EC, external capsule; F, forceps; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; OR, optic radiation; PLIC, posterior limb of internal capsule; PTR, posterior thalamic radiation; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; WM, white matter.

hemisphere, a cluster comprised of 2842 voxels and a cluster of 861 voxels also included parietal, temporal, frontal, and occipital WM and association, projection, and inter-hemispheric pathways. No significant decreases in FA with age were observed. Findings were most significant in the left SLF, temporal ILF, frontal IFOF, and frontal ATR ($P < .025$, corrected). An asymmetry in the distribution of FA changes was also reflected in the number of significant voxels per hemisphere: in the left hemisphere, a total of 13 523 voxels showed a significant relationship with age, and in the right hemisphere, 4046 voxels. To explore asymmetry in strength of the age-FA associations, we correlated mean FA of the significant voxels in the left hemisphere and the right hemisphere with age. Correlations for the left hemisphere ($r = .691$, $P < .001$) and the right hemisphere ($r = .592$, $P < .001$) were significantly different (Steiger procedure; $t = 2.96$, $P = .004$).

Meta-Analysis

Seven identified studies met the inclusion criteria for the meta-analysis. One study was excluded because this study did not report direct age-FA correlations, but a voxel-wise "developmental timing quotient."[26] One study was excluded because the subjects of that study showed complete overlap with a previous study.[13,27] Thus, 5 studies were included in the meta-analysis (see table 2).[13–17]

Table 2. Studies Included in Meta-Analysis of Diffusion Tensor Imaging Studies on Healthy White Matter Development

Study	Age		*N*	Sex (% F)	Magnetic Field Strength	Slice Thickness (mm)	Diffusion Directions
	Mean ± SD	Range					
Asato et al[15]	15.5 ± 4.5	8–28	114	55	3T	4	6 (NEX = 14)
Bava et al[14]	17.8 ± 1.4	16–21	22	32	3T	3	15 (NEX = 4)
Brauer et al[16]	7.0 ± 1.1; 27.8 ± 2.7[a]	6–9; 24–32	20	50	3T	1.7	60
Giorgio et al[13]	16.0 ± 1.8	13.5–21	42	48	1.5T	2.5	60
Qiu et al[17]	10.3 ± 0.5 22.8 ± 2.3[a]	9–12; 19–26	51	47	3T	3	6 (NEX = 4)

Note: NEX, number of excitations; F, Female.
[a]Mean age for 2 separate age groups with a bimodal age distribution.

Table 3. White Matter Clusters Showing a Positive Association Between Age and Fractional Anisotropy in a Meta-Analysis of Studies on Healthy Adolescent Development (Zucker Hillside data not included)

Cluster	Peak-Coordinate (MNI *x*, *y*, *z*)	Cluster Size (voxels)	*Z*-value	*P*-Value[a] (uncorrected)	White Matter Area/Tract
1	41, −20, 33	79	3.9	<.00001	Superior Longitudinal Fasciculus, Right
2	−37, −15, 27	71	3.6	.00001	Superior Longitudinal Fasciculus, Left
3	48, −19, −20	33	3.4	.00008	Inferior Longitudinal Fasciculus, Right
4	−16, 16, −2	22	3.3	.00015	Anterior Limb of Internal Capsule/Anterior Thalamic Radiation, Left
5	−45, −12, −27	28	3.2	.00033	Inferior Longitudinal Fasciculus, Left
6	12, 2, 5	17	3.1	.00071	Posterior and Anterior Limbs of Internal Capsule/Anterior Thalamic Radiation, Right
7	−9, 7, 27	11	3.0	.00119	Cingulate/Corpus Callosum, Left
8	−16, −7, 4	15	2.9	.00171	Posterior Limb of Internal Capsule, Left

[a]*P* values were obtained with a permutation test.

Asato et al[15] performed group-comparisons of different age groups as well as continuous age-FA correlations across all subjects. We used the peak coordinates of the latter analysis.

Meta-analysis of these 5 studies showed significant FA increases in the fronto-parietal sections of the bilateral SLF, bilateral ILF, bilateral ALIC (mainly in the left hemisphere) containing the ATR, left cingulate/body of the CC, and bilateral PLIC (see table 3). We note here that the ILF runs in close proximity to the IFOF in this part of the temporal lobe, and therefore, this cluster may have included some inferior parts of the IFOF. Of the identified 8 clusters, the cluster in the right PLIC and ALIC/ATR and the cluster in the left cingulate/body of the CC did not correspond to regions found in our sample. The other 6 clusters corresponded closely with regions identified in our sample. When the results from our sample were included in the meta-analysis, the results were the same regarding location, size, and significance of the clusters, with the exception that the cluster in the left cingulate/body of the CC was no longer significant.

There was no asymmetry observed in the distribution of the significant clusters in the meta-analysis, except for few more significant voxels in the left ALIC as compared with the right ALIC.

Sensitivity analyses showed that the identified WM tracts were consistent across the different studies. The bilateral SLF was highly consistent, independent from any individual study being discarded and comprised the 2 largest clusters (see figure 1B). The left ILF was no longer significant when the largest study was excluded from the analysis,[15] and the right ILF and right ALIC and PLIC were no longer significant when either the largest study or 1 study with medium sample size was excluded.[13,15,17] The left ALIC was no longer significant when either of the studies with medium sample sizes was excluded[13,17] as well as the left PLIC when 1 of these studies was excluded.[17]

Neurocognitive Correlates of SLF Development

As the SLF was the most consistent and robust finding in our sample and in the meta-analysis, we assessed the relationship between FA of the SLF and neurocognitive functions, which have previously been related to SLF WM integrity: verbal fluency (controlled oral word association test),[28] reading ability (WRAT-3),[29] vocabulary (WASI vocabulary score),[30] verbal working memory (UMd letter-number span),[6,31] and spatial working memory (Wechsler Memory Scale 3 spatial span).[32] The left and right SLF were tracked in each subject with probabilistic tractography,[24] by placing a seed region in the frontal part of the SLF (just anterior to the precentral gyrus), a way point in the frontal SLF just posterior to the seed region, a second way point in the middle temporal gyrus (MTG), and an exclusion mask that terminated fibers running anterior to the seed region, inferior to the way point in the MTG, or into MTG gray matter. The bilateral SLF of each subject was then thresholded at a normalized probability value of .01 (see figure 2A). FA-neurocognition relationships could not be assessed in all subjects due to either failure of the probabilistic tractography algorithm ($n = 12$) and/or missing neurocognitive data ($n = 14$ for verbal fluency; $n = 12$ for reading ability, verbal working memory, and spatial working memory; and $n = 18$ for vocabulary).

As results were similar for the left and right SLF, results are presented for mean FA of the bilateral SLF. FA of the SLF significantly predicted verbal fluency ($\beta = .436$, $t = 3.6$, $P = .001$; $n = 56$) and verbal working memory performance ($\beta = .313$, $t = 2.5$, $P = .018$; $n = 57$). There were trends for FA to predict reading ability

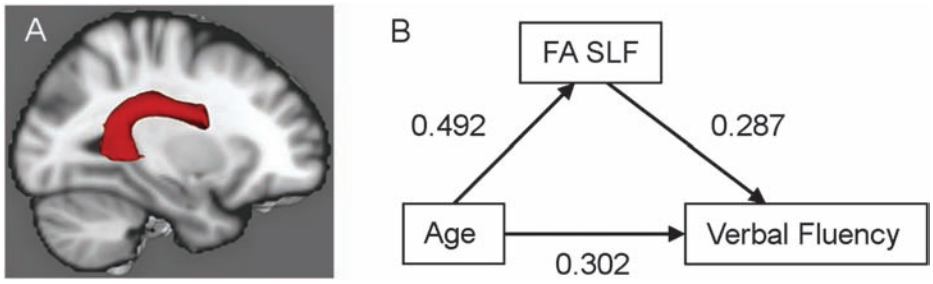

Fig. 2. Panel A: Left superior longitudinal fasciculus (SLF) as visualized with probabilistic tractography; averaged from 66 healthy subjects 8–21 years old, and overlaid on the MNI152 T1 template for display purposes. Panel B: Fractional anisotropy (FA) of the bilateral SLF partially mediated an observed relationship between age and verbal fluency. Strength of the relationships is indicated by the standardized regression coefficients ($P < .05$). Age and FA of the SLF were both significant predictors of verbal fluency performance, but the coefficient for age was reduced from .443 to .302 by the presence of the SLF, which in turn was a significant predictor of verbal fluency independent of the age effect.

(β = .257, t = 2.0, P = .053; n = 57) and spatial working memory performance (β = .227, t = 1.7, P = .089; n = 57) but not vocabulary ($P > .1$; n = 51). Next, verbal fluency and verbal working memory performance were each entered into a separate mediation model with age and FA as predictor variables. FA of the SLF partially mediated increases in verbal fluency as a function of increasing age: (1) age was a significant predictor of verbal fluency (β = .443, t = 3.6, P = .001), and this association was reduced when FA of the SLF was added to the model (β = .302 t = 2.2, P = .030); (2) FA was a significant predictor of verbal fluency independent of the age effect (β = .287, t = 2.1, P = .039) (see figure 2B and figure 3). Age was also a significant predictor of verbal working memory performance (β = .513, t = 4.4, $P < .001$), but FA of the SLF was not a predictor of verbal working memory performance independent of the age effect (β = .071, t = 0.5, P = .604).

Because language function has been associated with structural lateralization, we explored the effects of lateralization of the SLF on the examined language-related measures (ie, verbal fluency, verbal working memory, reading ability, and vocabulary). Lateralization of FA values in the SLF ([FA left SLF − FA right SLF]/[FA left SLF + FA right SLF]/2) was not significantly associated with these measures ($P > .1$). When the analysis was restricted to right-handed subjects (Edinburgh lateralization index > 0.7), there appeared a trend for lateralization to predict poorer verbal working memory performance (β = −.286, t = −1.9, P = .067).

Discussion

We report bilateral increases in FA with age in a large sample of healthy children, adolescents, and young-adults, with an asymmetric distribution favoring the left hemisphere. This is consistent with previous DTI-TBSS studies that have investigated WM development from childhood into early adulthood, although the identified WM tracts partially vary between our and other studies.[13–17] This variation in findings may be related to the differences in age range of included subjects, DTI methodology, and interindividual differences in WM development. We therefore performed a meta-analysis of these studies to identify which fiber tracts show the most pronounced development across adolescence. The meta-analysis identified increases in FA that were most consistent and robust in the bilateral SLF and less consistent in the bilateral ILF, ALIC/ATR, and PLIC. A left > right asymmetry of age effects on FA was not confirmed by the meta-analysis.

These results concur with findings of DTI studies that have utilized other analysis approaches than TBSS to study healthy WM development. Several DTI tractography studies have also observed FA increases from childhood into early adulthood in the SLF,[27,33,34] ILF,[27,34] ALIC,[33] and ATR.[34] In conventional VBA studies, the most consistently identified tracts of change between childhood and early adulthood were the left SLF and the bilateral PLIC.[10,11] A pronounced FA increase in the SLF during adolescence concurs with the cross-sectional analysis by Lebel et al[33] who calculated that, while FA values of the major WM tracts reach their plateau at different age periods, the SLF peaks between 15 and 20 years of age. The uncinate fasciculus and the cingulate were calculated to mature last in early adulthood.[33] Therefore, it may be considered unexpected that we did not identify significant changes in these tracts. This apparent discrepancy may be related to the mean age and age range of the included samples, which focused the present study on detecting FA changes in middle to late adolescence. In a longitudinal follow-up study, Lebel et al[35] confirmed substantial FA increases in the SLF between 8 and 22 years of age, while the uncinate showed much less FA increases during this period and the cingulate somewhat more increases than the uncinate but to a lesser extent than the SLF. This observed protracted development of the uncinate fasciculus and cingulate with more gradual FA increases from childhood into early adulthood suggests, together with our results, that adolescence is not a key period in which these tracts undergo active development.

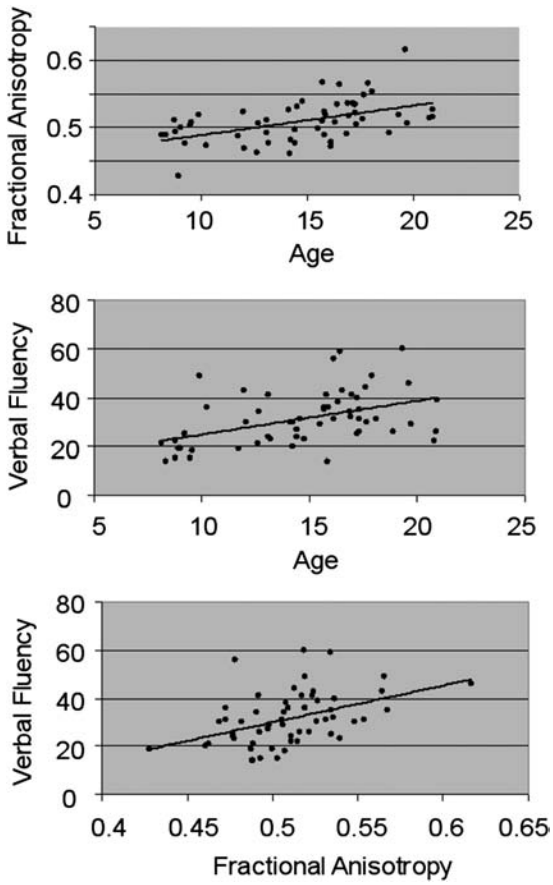

Fig. 3. Correlations between fractional anisotropy of the superior longitudinal fasciculus, age, and verbal fluency in 8- to 21-year-old healthy subjects. Top panel: age significantly predicted FA of the SLF ($\beta = .492$, $t = 4.3$, $P < .001$; $n = 56$). Middle panel: age significantly predicted verbal fluency (not adjusted for FA; $\beta = .443$, $t = 3.6$, $P = .001$; $n = 56$). Bottom panel: FA was a significant predictor of verbal fluency (not adjusted for age; $\beta = .436$, $t = 3.6$, $P = .001$; $n = 56$).

We tested for neurocognitive correlates of the SLF in our sample to identify which cognitive functions the SLF serves during healthy development. Among 5 neurocognitive tests in the domains of language and working memory, FA of the SLF was significantly associated with performance on a verbal fluency test and partially mediated increases in verbal fluency as a function of increasing age. This finding is in agreement with a previous DTI study in young adults that found an association between SLF WM integrity and verbal fluency.[28] Indeed, there is substantial evidence from neuroimaging studies that the SLF plays a critical role in human language development. For example, Brauer et al[16] found in healthy adults that the SLF connects the language areas of Broca and Wernicke, while in children, the language network also included a ventral pathway through the external capsule, suggesting that language development is paralleled by maturation of the SLF. Moreover, in children with dyslexia, improvement in reading skills was predicted by higher FA in the right SLF, compared with children without dyslexia.[29] In our sample, higher FA of the SLF predicted better reading ability at trend level but did not predict vocabulary score, in contrast with a previous DTI study in healthy children.[30] Three segments of the dorsal language network have been identified with DTI tractography in healthy adults, consisting of a ''direct'' pathway between Wernicke's and Broca's area (ie, the SLF) and 2 ''indirect'' segments in close proximity to the direct pathway, connecting Broca's area with the inferior parietal lobe (IPL) and the IPL with Wernicke's area.[36] The SLF as obtained with our tractography algorithm most likely comprised the direct pathway because this pathway runs continuously from frontal to temporal, corresponding with our frontal seed region and temporal way point.

FA of the SLF did not predict spatial working memory performance in our sample, contrary to another DTI study in healthy children.[32] We did observe an association between verbal working memory performance and FA of the SLF, which is consistent with previous DTI studies that have implicated the SLF in verbal working memory performance in healthy children, adolescents, and young adults.[6,31] Working memory may be served by other components of the SLF than those associated with language.[37] A detailed tractography study of the SLF in healthy adults identified 2 subcomponents of the SLF additional to the central core of the SLF (as measured in our study), which connect several parietal and frontal areas including the dorsolateral prefrontal cortex.[37] In our sample, FA of the SLF was no longer a significant predictor of verbal working memory performance after adjusting for age. This is an important dilemma in developmental studies: increases in neurocognitive performance potentially correlate with growth of neural structures simply because of their association with age, yet correcting for age leads to the association with brain structure being covaried out.

We found little effect of lateralization of FA values of the SLF on measures of language function. Catani et al[36] found in healthy adults that leftward lateralization of the reconstructed fibers of the SLF was associated with lower verbal recall score. These results indicate that language function is not significantly associated with lateralization of FA in the SLF, while a more symmetric distribution of SLF fibers may be advantageous for remembering words.

The SLF has been implicated in the pathophysiology of schizophrenia, and our results suggest that abnormal development of the SLF during adolescence may play a key role in the pathophysiology of the disorder. In patients with first-episode or recent-onset schizophrenia and patients at clinical high risk for psychosis, reduced FA was identified in the SLF and correlated with poorer verbal working memory performance in recent-onset patients.[6,7,38] Higher FA values in the SLF have been related to auditory hallucinations in chronic patients.[39]

A key role for the SLF in schizophrenia is consistent with its role in working memory and language, as these faculties are significantly compromised in patients and their relatives.[40,41] Indeed, it has been proposed that the emergence of language during human evolution has been fundamental to the evolution of schizophrenia.[42]

A possible limitation of our meta-analysis are the differences in age range between the studies. Nonetheless, despite these differences, all studies included the period of late adolescence/early adulthood. A second limitation is the limited number of TBSS studies that were available for the meta-analysis. A significant strength of our meta-analysis, however, is that original *t* statistic maps were available for most of the included studies, thus allowing significantly more accurate results than if estimations had been conducted from only a few reported peak coordinates. The *t* statistic images were not available for 2 studies,[15,16] but in the validation study of ES-SDM, it was found that including *t* statistic images for as few as 10%–20% of the studies greatly enhances the sensitivity of the meta-analysis.[21] In addition, our meta-analysis is, to our knowledge, the first-ever method and template to conduct meta-analyses of TBBS studies. We have included this approach in the ES-SDM software to allow colleagues conduct such meta-analyses.

In conclusion, DTI has provided valuable insights into healthy WM development in adolescence. Findings with TBSS highlight increasing connectivity in the SLF during this period and implicate the SLF as a specific target for neurodevelopmental disorders such as schizophrenia. The functional correlates of WM changes remain a critically understudied area, especially regarding the cognitive, emotional, and behavioral changes that occur in adolescence. Our results confirm the role of the SLF in language development and to some extent in verbal working memory. Other important future areas of investigation concern those genes that play a role in WM maturation, and how risk genes may contribute to development of WM abnormalities. Large studies applying multimodal imaging, combined with genomics and comprehensive clinical and neurocognitive assessments can answer these questions. Moreover, longitudinal designs will have greater power to provide more insight into the WM trajectories that may contribute to neurodevelopmental disorders.

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