Superior longitudinal fasciculus and cognitive dysfunction in adolescents born preterm and at term

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Abstract

Aim—To understand the relation between cognition and white matter structure in adolescents born preterm without obvious brain injury.

Methods—Thirty-two adolescents were selected based on birth risk (Full-term: M:F=8:5, Median (Interquartile Range) Age=16.1(0.8); Low-risk preterm: M:F=4:5, Age=16.0(0.3); High-risk preterm: M:F=3:7, Age=16.2(1.2)) and reading ability (Good-readers: M:F=3:8, Age=16.0(0.6); Average-readers, M:F=6:3, Age=16.8(1.0); Poor-readers M:F=6:6, Age=16.0(0.5)) from a longitudinal study on child development. Preterm birth was defined as a gestational age ≤36 weeks and a birth weight ≤1600g. All participants demonstrated normal clinical neuroimaging. We examined fractional anisotropy (FA), radial diffusivity and volume of three major white matter fasciculi. The relations between structural measures and birth risk, hemisphere and cognitive ability (attention, lexical and sublexical decoding, auditory phonological awareness and processing speed) were analyzed using mixed-model regression.

Results—Left superior longitudinal fasciculus (SLF) FA and radial diffusivity was related to reading-related skills while right SLF FA was related to attention skills. SLF volume decreased as these skills declined for adolescents born preterm, but not those born at term.

Interpretation—The relation between cognitive skills and SLF volume suggests that cryptic white matter injury may exist, possibly related to oligodendrocyte or axonal loss, despite normal clinical neuroimaging in adolescents born preterm.

Keywords

Diffusion Tensor Imaging; Prematurity; Cognitive dysfunction

Introduction

Children born preterm, as compared to those born at term, are more likely to require special assistance and to be diagnosed with a specific learning disability despite adequate intelligence. For example, school-age children with a history of preterm birth have deficits...
in executive function\textsuperscript{1}, visuospatial skills\textsuperscript{1}, and early language development \textsuperscript{2}. At this time, the relation between brain anatomy and neuropsychological and achievement deficits is unclear.

Over the past two decades we have studied the development of a large cohort of children who were born at term and preterm. Children born preterm were recruited to represent those who were at low-risk and high-risk for developmental difficulties based on their medical complications during the neonatal period. We recently investigated the relation between verbal, non-verbal and executive function skills and reading during the 3\textsuperscript{rd}, 5\textsuperscript{th} and 7\textsuperscript{th} grades in this cohort\textsuperscript{3}. Participants were divided into three reading ability groups based on the levels and growth of the Woodcock-Johnson Test of Achievement Word Attack subtest (WA) during the study period. Children born preterm were found not to be more likely to be poor readers, but children born preterm at high-risk with poor reading ability, as compared to other groups, were found to perform poorly on executive function tasks, particularly on the inattention index of a continuous performance task (CPT).\textsuperscript{4} This suggests that poor readers born preterm at high-risk may represent a group of children with more severe cognitive dysfunction.

Anatomic neuroimaging has revealed selective disturbances in microstructure of the deep white matter tracts and the longitudinal fasciculi in children born preterm who do not show obvious brain injury on prenatal, perinatal or neonatal ultrasound\textsuperscript{5}. Attention deficit in preterm children has been linked to microstructure of the inferior and superior longitudinal fasciculi, and inattention has been correlated with microstructure of the superior fasciculi\textsuperscript{5}. The superior longitudinal fasciculus (SLF) may be especially important during child development, since, in addition to being related to inattention\textsuperscript{5}, it connects cortical regions of the brain involved in reading\textsuperscript{6} and diffusion tensor imaging (DTI) has implicated white matter disorganization of this fasciculus in individuals with reading disability\textsuperscript{7}. Thus, we believe that this pathway may be specifically affected in poor readers born preterm at high-risk. Such a finding would support our behavioral link between poor reading and executive dysfunction in children born preterm at high-risk. In this article we use an atlas-based DTI algorithm to examine the relation between the microstructure and macrostructure of the longitudinal fasciculi to birth risk (i.e., term, low-risk, high-risk) and two important aspects of cognitive function, reading-related skills and attention, in a subsample of our previously studied cohort\textsuperscript{3}.

Method

The Original Cohort

Our original longitudinal cohort contained 360 children recruited from three hospitals in the greater Houston area. Inclusion and exclusion criteria for preterm and term participants and high-risk and low-risk preterm participants are provided in Tables S1 and S2. Most participants were African-American (63.0\%) with fewer being of Caucasian (20.1\%) and Hispanic (15.0\%) ethnicity. The sample contained predominately lower social economic status (SES) participants. There were slightly more females than males. Quality of schooling, SES, gender and ethnicity were not different across birth groups.

The Reading Study Participants

Recently we studied the relations between language, intelligence and executive function and reading ability and birth status during the 3\textsuperscript{rd}, 5\textsuperscript{th} and 7\textsuperscript{th} grades in the original cohort. Participants were clustered into poor, average, and good readers by analyzing the level and growth of phonological word decoding as indexed by WA\textsuperscript{8} (See Table S3). Sixteen participants from the original cohort were eliminated because they demonstrated two or
more Stanford-Binet 4th Ed. quantitative skill scores below 85. Because of attrition, 91 participants of the original group could not be assigned a reading group. This resulted in a total of 253 participants, 70.3% of the original cohort.

The Adolescent Sample

In order to study brain-behavior relations in a group of adolescents with a wide-range of reading abilities we attempted to recruit five participants from each reading group and birth risk combination evenly distributed across gender. Reading grouping was not used further; rather the actual reading-related skills were analyzed in the current study. Right-handedness was confirmed by a laterality index as assessed by the Edinburgh Handedness Inventory score greater than 50\(^9\). After description of the study, written informed consent was obtained in accordance with our Institutional Review Board regulations for the protection of human subjects. Thirty-two participants underwent a reading assessment and DTI scan. Inattention was derived as the average CPT inattention score across the 3rd, 5th and 7th grades. Twenty of the adolescents underwent the Test of Variables of Attention (TOVA), an alternative continuous performance test, during the time of the reading assessments. The standardized attention score of the TOVA correlated \(r=0.43\) (\(t(18)=2.02\), \(p<0.05\)) with the inattention score from the CPT. Characteristics of the final sample are given in Table 1.

Reading Assessment

Participants were tested on carefully selected tests to assess targeted reading-related skills. Orthographic lexical and sublexical decoding was measured with the Woodcock-Johnson III Letter-Word Identification subtest and WA, respectively. Pure auditory phonological awareness skill and speed of retrieval was measured by the Comprehensive Test of Phonological Processing Phoneme Reversal and Rapid Naming Composite, respectively.

MRI and DTI Data Acquisition and Processing

We utilized a high signal-to-noise ratio whole-brain DTI protocol at 3.0T that was kept under 7 minutes\(^11\). The diffusion-weighted data were collected axially (inferior-to-superior from the foramen magnum to the vertex) using 44 contiguous 3 mm sections that covered the entire brain. The diffusion sensitization or b-factor was 1000 s mm\(^{-2}\) and the encoding scheme used 21 uniformly distributed directions. Details of the DTI image processing and data quality control measures are provided elsewhere\(^11\). Anatomical T1 and T2 images were also acquired and reviewed by a board-certified radiologist and/or neurologist. One abnormal scan was excluded.

After diffusion-weighted data preprocessing which included distortion correction, masking and isotropic voxel interpolation, the diffusion tensors were constructed and diagonalized as described elsewhere\(^11\). The tensor eigenvalues were used to obtain the transverse, principal, mean diffusivities as well as volumes. Gray and white matter was segmented using a DTI-based algorithm\(^12\). Fiber tracts were automatically segmented using the statistical parametric mapping toolbox (http://www.fil.ion.ucl.ac.uk/spm) and the international consortium for brain mapping probabilistic templates and atlases as described in Mori et al\(^13\). Measures used in this manuscript include the mean pathway fractional anisotropy (FA) and radial diffusivity (RD) and pathway volume normalized by total intracranial volume. For this study we specifically identified and analyzed the SLF and the superior and inferior frontal-occipital fasciculi.

Statistical Analysis

A general linear mixed-model (‘mixed’ procedure of SAS 9.1, SAS Institute Inc., Cary, NC), was used to investigate the relations between the fixed-effects of birth group,
hemisphere and cognitive skill and the white matter indices (FA, RD, Volume). The intercept was modeled as a random-effect. The full linear model is given in Equation (1). Before calculating the full model a reduced model that did not include the cognitive skill was calculated to investigate the effect of birth group and hemisphere on white matter structure. The full model was calculated for each cognitive skill separately.


Models were simplified hierarchically by removing the highest-order non-significant interaction or fixed-effect if all interaction containing it were eliminated. The model was simplified until an interaction was significant, in which case all effects contained within the interaction were retained, or all effects in the model were significant. This statistical simplification procedure is commonly used, including in our previously behavioral and brain imaging studies3,14. Since we made multiple comparisons using the same structural measure (i.e., five behavioral performance variables) we set out alpha to 0.01 for the full analysis. However, an alpha of 0.05 was used for the initial reduced analysis that did not include cognitive skills. To better understand the relations between cognitive skills and microstructure when interactions were present, we used Pearson correlation statistics for each group separately. This was done for descriptive purposes with the caveat that correlation analysis was less sensitive than the interaction due to the reduced sample size relative to the total sample. When the hemisphere effect or its interaction was not significant, the microstructure measurements were averaged across hemisphere before graphing or performing correlations in order to mitigate the effect of repeated observation.

Results

Non-performance associated effects

Superior longitudinal fasciculus—Neither FA nor RD was different across birth groups. RD was larger in the right as compared to the left hemisphere [F(1,30)=19.69, p<0.01] (Figure 1B). FA was not different across hemispheres.

Superior frontal-occipital fasciculus—The relation between FA and birth group was different across hemispheres [F(2,28)=4.54, p=0.02]. FA became increasingly different across hemispheres as birth-risk increased from term to low-risk to high-risk. RD was not influenced by either birth group or hemisphere (Figure 1C). Volume was greater in the right, as compared to the left, hemisphere [F(1,31)=40.97, p<0.01] but was not different across birth groups.

Inferior frontal-occipital fasciculus—The relation between FA and birth group was different across hemispheres [F(2,29)=5.09, p=0.01]. As seen in Figure 1E FA was higher in the left, as compared to the right, hemisphere for term adolescents, equal across hemispheres for adolescents born preterm at low-risk and greater in the right, as compared the left, hemisphere for adolescents born preterm at high-risk. Interestingly, this difference across hemisphere was driven by changes in FA for the left but not the right hemisphere. RD was significantly smaller in the left, as compared to the right, hemisphere [F(1,31)=10.35, p<0.01; Figure 1F].
Performance associated effects that differ across hemispheres

Superior longitudinal fasciculus—The relation between FA and letter-word identification [F(1,30)=20.03, p<0.01], phoneme reversal [F(1,30)=6.69, p=0.01] and inattentiveness [F(1,30)=8.68, p<0.01] was different across hemispheres. The relation between FA and performance on letter-word identification [r(30)=−0.37, p<0.05] and phoneme reversal [r(30)=−0.34, p=0.05] was significant in the left, but not the right, hemisphere (Figure S1A,B) while the relation between inattentiveness and FA was significant in the right [r(30)=−0.38, p<0.05], but not the left, hemisphere (Figure S1C). FA decreased as task performance increased for all cognitive tasks.

The relation between RD and performance on letter-word identification [F(1,30)=6.39, p=0.01] and phoneme reversal [F(1,30)=7.82, p<0.01] was different across hemispheres with the relations between left, but not right, hemisphere RD and performance on the letter-word identification [r(30)=0.31, p<0.10] and phoneme reversal [r(30)=0.40, p<0.05] being significant or near significance (Figure S1D,E). RD increased as task performance increased for all cognitive tasks.

Performance associated effects that differ across birth groups

Superior longitudinal fasciculus—Volume was not different across birth groups or hemispheres. The relation between volume and phoneme reversal [F(2,32)=4.90, p=0.01] and inattention [F(2,32)=5.32, p<0.01] were different across birth groups. Reduced SLF volume was associated with poorer performance on phoneme reversal for the all adolescents born preterm [r(17)=0.58, p<0.01]. This relation was significant for adolescents born preterm at high-risk [r(9)=0.70, p<0.02] and near significant for adolescents born preterm at low-risk [r(6)=0.63, p<0.10] whereas there was no relation for adolescents born at term (Figure 2A). Reduced SLF volume was associated with higher inattention for all preterm born adolescents [r(17)=−0.69, p<0.01] with this relation significant for adolescents born preterm at high-risk [r(9)=−0.77, p<0.01] but not adolescents born preterm at low-risk when the risk groups were analyzed separately. Interestingly, adolescents born at term demonstrated the opposite relation; increased SLF volume was associated with greater inattentiveness [r(11)=0.59, p<0.05] (Figure 2B).

Discussion

In this study we examined the brain-behavior relations between reading-related and attention skills and structural characteristics of white matter tracts that connect the frontal lobes with posterior areas of the brain (i.e., parietal, temporal and occipital lobes) in adolescents born at term and preterm at low-risk and high-risk. Specifically, we examined the microstructure and macrostructure of the SLF and superior and inferior frontal-occipital fasciculi. Our findings suggest that the microstructure of the SLF may be related to reading-related and attention skills with this relation demonstrating different lateralization depending on the skill. The two reading-related tasks, letter-word identification and phoneme reversal, were related to left SLF microstructure, while the attention skill was related to right SLF microstructure. This relation was not different across birth groups suggesting that changes in SLF microstructure may represent a general neuropathological marker of cognitive dysfunction. In contrast, the relation between SLF macrostructure and cognitive function was different across birth groups. Specifically, poorer performance on reading-related and attention tasks was related to a reduction in SLF volume in adolescents born preterm but in not adolescents born at term. This suggests that common microstructural changes seen in both adolescents born preterm and at term may arise from different developmental processes. A relationship between cognitive skills and the frontal-occipital fasciculi structure was not found in this study. Unlike the SLF, the microstructure of the frontal-occipital
fasciculi was influenced by birth risk, possibly adding variability to the microstructure measures, resulting in poor brain-behavior correlations.

Animal, genetic and imaging studies have converged on abnormalities in brain connectivity underlying reading disability. Genes associated with reading disability appear to be linked to neural migration and axonal guidance. Both functional and anatomic neuroimaging studies suggest abnormal connectivity between language areas in individuals with reading disability. Our data is consistent with the notion that the SLF is important in reading. This pathway connects cortical regions hypothesized to be involved in reading and at DTI studies has implicated white matter disorganization of the SLF in reading disability. The current study suggests that the microstructure of the SLF is similarly disrupted in adolescents born at term and preterm.

We have demonstrated that better performance on certain reading-related tasks was associated with a lower FA and higher RD in the SLF. These patterns of microstructure changes are consistent with previous studies examining the corpus callosum and the temporoparietal white matter. Dougherty et al. suggested that this effect could be due to differences in the type and size of the axons. Specifically, a higher FA and lower RD could be consistent with a decrease in the number of larger diameter fast axons. Such a notion would certainly be consistent with the neuropathological loss of magnocellular neurons and increased latencies of evoked responses documented in individuals with reading disability. However, other alternative interpretations are equally probable. For example, a lower FA, especially calculated on the whole pathway volume, might indicate a simpler white matter pathway with less crossing fibers. Further research will need to differentiate these multiple possibilities.

The data from this study suggests that microstructure of the right SLF is related to inattention. The relation between poor connectivity linking the posterior and anterior brain and poor performance on the CPT is consistent with functional imaging studies. Functional imaging has confirmed that frontal brain areas, including the inferior, middle superior, orbital areas, participate in an extensive brain-wide neural network during the CPT. The fact that our previous study demonstrated an association between reading and executive function in children born preterm at high-risk is consistent with neuroimaging studies on preterm children that suggest a general disconnection between the anterior and posterior brain region. Preterm children demonstrate abnormal microstructure in white matter pathways connecting frontal and parietal, temporal and occipital areas and reduced modulation of frontal areas during a passive auditory language listening task. Indeed, individuals born preterm may find it difficult to recruit frontal brain areas during reading and executive function tasks. For example, functional imaging studies have suggested that children born preterm use alternative strategies to process language that may not require frontal brain areas such as overly relying on semantic information.

Volume of the SLF was found to be related to performance on a reading-related and attention task for adolescents born preterm, but not term. This finding is consistent with known neuropathology associated with preterm birth. Indeed, neuropathological studies have suggested that white matter volume loss in very low birth weight preterm infants is associated with axonal and/or oligodendrocytes loss. DTI studies have demonstrated patterns of microstructure abnormalities consistent with axonal and/or oligodendrocytes loss in wide spread white matter areas. This suggests the neuropathology associated with cognitive dysfunction in adolescents born preterm is much more severe than the neuropathology associated with equivalent cognitive dysfunction in term adolescents. This also suggests that clinical scans may not be sensitive enough to detect these subtle changes.
and quantitative methods may be useful in the future for predict cognitive dysfunction in adolescents born preterm.

In this manuscript we focused on white matter correlates of cognitive dysfunction in a population of adolescents born preterm and term. We found both similarities and differences between adolescents born preterm and at term in the association between white matter structure and reading and attention. Understanding the structural changes that underlies poor reading in adolescents born preterm should help delineate how to better target remediation and medical therapies, both at birth and throughout life. Identifying the neuroimaging signature of white matter damage associated with cognitive dysfunction in adolescents born preterm may provide a biomarker for identifying adolescents born preterm at risk for cognitive dysfunction.

This study presents a starting point for larger studies which can examine additional important factors that might influence brain development such as participant gender. Future studies should also attempt to stratify across gender in order to provide a more balanced sample. This study and our previous studies have demonstrated that spoken and written language and executive function are important cognitive domains to study in children born preterm. More extensive achievement and neuropsychological batteries performed at the time of MRI acquisition would be optimal. Based on the analysis from this study we have estimated the necessary sample size to achieve this goal. We used linear regression to estimate the $r^2$ for the mixed-model analysis outlined above. The $r^2$ ranged from 0.10 to 0.39. This corresponded to an effect size of 0.11 to 0.64. Given this effect size and a linear model that includes gender, birth risk and cognitive performance with an alpha of 0.01 and power of 95%, a sample size from 66 to 311 would be needed, depending on the structural measure being analyzed.

What this paper adds

- Adolescents born term and preterm have similar white matter microstructure abnormalities related to cognitive deficits.
- Adolescents born preterm, but not those born term, have white matter macrostructural abnormalities despite normal clinical neuroimaging.
- Macrostructural abnormalities in adolescents born preterm are related to cognitive deficits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study has not been presented or published previously.

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References


Figure 1.
(A,C,E) Fractional anisotropy and (B,D,F) radial diffusivity of the (A,B) superior longitudinal fasciculus and the (C,D) superior and (E,F) inferior frontal-occipital fasciculi. Radial diffusivity was lower in the left as compared to the right hemisphere. Radial diffusivity units are $\mu m^2 / sec \times 10^{-3}$. Error bars indicate standard errors.
Figure 2.
(A,B) The relationship of the superior longitudinal fasciculus volume (normalized to total white matter volume) to phoneme reversal and inattentiveness for children born at term and prematurely at low and high risk. (C) The relationship between superior frontal-occipital fasciculus volume (normalized to total white matter volume) and hemisphere.
Table 1
Participant Characteristics. Median (interquartile range)

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<th>Birth Group</th>
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<td>Male : Female</td>
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<td>Gestational Age</td>
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<td>Birth Weight</td>
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<td>Letter-Word Identification</td>
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<td>Rapid Naming Composite</td>
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<tr>
<td>Inattention</td>
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