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Preterm Birth Results in Alterations in Neural Connectivity at Age 16 Years

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Abstract

Very low birth weight preterm (PT) children are at high risk for brain injury. Employing diffusion tensor imaging (DTI), we tested the hypothesis that PT adolescents would demonstrate microstructural white matter disorganization relative to term controls at 16 years of age. Forty-four PT subjects (600 - 1250 grams birth weight) without neonatal brain injury and 41 term controls were evaluated at age 16 years with DTI, the Wechsler Intelligence Scale for Children - III (WISC), the Peabody Picture Vocabulary Test - Revised (PPVT), and the Comprehensive Test of Phonological Processing (CTOPP).

PT subjects scored lower than term subjects on WISC full scale ($p = 0.003$), verbal ($p = 0.043$), and performance IQ tests ($p = 0.001$), as well as CTOPP phonological awareness ($p = 0.004$), but scored comparably to term subjects on PPVT and CTOPP Rapid Naming tests. PT subjects had lower fractional anisotropy (FA) values in multiple regions including bilateral uncinate fasciculi (left: $p = 0.01$; right: $p = 0.004$), bilateral external capsules (left: $p < 0.001$; right: $p < 0.001$), the splenium of the corpus callosum ($p = 0.008$), and white matter serving the inferior frontal gyrus bilaterally (left: $p < 0.001$; right: $p = 0.011$). FA values in both the left and right uncinate fasciculi correlated with PPVT scores (a semantic language task) in the PT subjects (left: $r = 0.314$, $p = 0.038$; right: $r = 0.336$, $p = 0.026$). FA values in the left and right arcuate fasciculi correlated with CTOPP Rapid Naming scores (a phonologic task) in the PT subjects (left: $r = 0.424$, $p = 0.004$; right: $r = 0.301$, $p = 0.047$).

These data support for the first time that dual pathways underlying language function are present in PT adolescents. The striking bilateral dorsal correlations for the PT group suggest that prematurely born subjects rely more heavily on the right hemisphere than typically developing

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adults for performance of phonological language tasks. These findings may represent either a delay in maturation or the engagement of alternative neural pathways for language in the developing PT brain.

Keywords

Preterm; adolescence; diffusion tensor imaging; dual language system

Introduction

Premature birth is a pressing public health matter, as nearly 13% of infants in the United States are born preterm and infants weighing under 1500 grams at birth comprise 1.5% of births (Beck et al., 2010; Martin et al., 2008). The brains of infants born prematurely face increased susceptibility to the challenges of ischemia and inflammation. Through the downstream effectors of excitotoxicity and free-radical attack, both glia and axons are disrupted, and the damage is compounded by secondary disturbance of growth patterns (Dyet et al., 2006; Hack et al., 2002; Miller et al., 2005). In addition to feared neurological complications of preterm birth such as cerebral palsy, a range of developmental deficits in cognitive function in preterm children have been observed to persist until early adulthood, indicating long-term disruption of brain function (Hack, 2009; Neubauer et al., 2008). Preterm children with severe brain injury such as periventricular hemorrhagic infarction and periventricular leukomalacia have the greatest risk of neurodevelopmental deficits; however, even those without these forms of brain injury are more likely than control term subjects to have lower IQ scores and require more support in language-based skills (Luu et al., 2009) during childhood and adolescence.

Recent investigations have proposed dual systems of language processing, analogous to dual pathways identified in visual processing (Friederici, 2009; Hickok and Poeppel, 2007; Saur et al., 2008). In this model, a ventral pathway processes comprehension of speech, with mapping of sounds to semantic representations, while a dorsal pathway is involved in matching speech signals to phonological and articulatory representations. The prototypical task calling upon the dorsal pathway is repetition, while the ventral pathway is vital in understanding meaningful speech. The arcuate fasciculus has been identified as the primary component of the dorsal pathway, while the ventral pathways are likely comprised of fibers traveling through both the extreme capsule and the uncinate fasciculus, a ventral pathway connecting the temporal and frontal lobes (Gozzo et al., 2009; Parker et al., 2005). The ventral pathway is thought to be bilateral, while the dorsal pathway tends to be strongly left-dominant (Hickok and Poeppel, 2007; Parker et al., 2005). Furthermore, since investigations of the dual pathway language systems have taken place in adult subjects, the developmental timing of specialization of these pathways is not fully understood. (Cao et al., 2009; Chou et al., 2006; Ment et al., 2006; Peterson et al., 2002).

Diffusion tensor imaging (DTI) provides a sensitive means of assessing the integrity of white matter tracts at a microstructural level. As part of DTI analyses, fractional anisotropy (FA) values provide a quantitative measure of the degree to which water diffusion is restricted along one axis relative to all others. Within cerebral white matter, water preferentially diffuses along axons, with diffusion perpendicular to this axis restricted by structural barriers including cell membranes. Higher FA values are a marker for the coherence of white matter tracts, as the constraints of the tissue organization into axon bundles within well-formed tracts limit the direction of water diffusion. Alterations in FA may result from changes in fiber organization, axonal size (Assaf et al., 2008), or activity-dependent changes in myelination (Als et al., 2004).

Previous studies have shown deficits in FA values in white matter tracts in premature infants at term-equivalent age as compared to term infants (Anjari et al., 2009; Anjari et al., 2007; Berman et al., 2005; Cheong et al., 2009; Dudink et al., 2007; Gimenez et al., 2008; Huppi et al., 1998; Huppi et al., 2001; Miller et al., 2002; Partridge et al., 2004; Rose et al., 2008), and changes in FA values can persist to late childhood and adolescence (Constable et al., 2008; Counsell et al., 2007; Counsell et al., 2008; Gimenez et al., 2006; Kontis et al., 2009; Murakami et al., 2008; Nagy et al., 2003; Reiss et al., 2004; Skranes et al., 2007; Vangberg et al., 2006; Yung et al., 2007). Moreover, FA values have been shown to correlate with multiple measures of neurodevelopmental function (Als et al., 2004; Arzoumanian et al., 2003; Bassi et al., 2008; Berman et al., 2009; Drobyshevsky et al., 2007; Krishnan et al., 2007; Peterson et al., 2000; Rose et al., 2009; Rose et al., 2007; Skranes et al., 2007).

Further, preterm children may develop language pathways differently than normally developing term children. For example, functional connectivity analyses have shown stronger connections between Wernicke's area and right-sided cortical regions in preterm children than in term children, implying changes in lateralization of language processing (Gozzo et al., 2009). This may represent increased utilization of compensatory alternative pathways in the right hemisphere in preterm children. Thus, for language tasks in particular, preterm children may engage alternative pathways, including increased utilization of the right hemisphere.

We hypothesize that preterm children at age 16 will continue to have deficits in both cognitive testing and microstructural integrity of multiple white matter tracts. By evaluating dorsal and ventral language pathways in preterm children, we will investigate whether preterm children demonstrate departures from the dual language pathway as described in typically developing adults, which may represent delays in maturation or compensations for changes in glio- and/or neurogenesis caused by the injury of preterm birth.

Methods

This study was performed at the Yale University School of Medicine, New Haven, CT and Brown Medical School, Providence, RI. The protocols were reviewed and approved by institutional review boards at each location. Children provided written assent; parent(s) provided written consent for the study. All scans were obtained at Yale University and were analyzed at Yale University and at Stanford University.

Subjects

The preterm cohort consisted of 44 children with no evidence for intraventricular hemorrhage (IVH), periventricular leukomalacia and/or low pressure ventriculomegaly. Subjects had normal findings on conventional MRI, and total ventricular CSF volume within 2 SD of the mean ventricular volume of term control subjects at 12 years of age. They had no contraindications to MRI. All preterm subjects enrolled in the follow-up component of the "Multicenter Randomized Indomethacin IVH Prevention Trial" (Ment et al., 1994a; Ment et al., 1994b) were sequentially recruited for the MRI study when they reached 16 years of age. These children are representative of the cohort of subjects with no evidence of neonatal brain injury with respect to gender, handedness, FSIQ scores, minority status, and maternal education. Forty-one healthy term children, aged 16 years, were recruited from the local community and group-matched with the PT as previously described.

The assessments of neonatal health status and neurologic outcome have been previously described (Peterson et al., 2000). Blinded assessment of intelligence was performed using the Wechsler Intelligence Scale for Children-III (WISC) (Vohr et al., 2003). Children also received the Peabody Picture Vocabulary Test -Revised (PPVT) (Dunn and Dunn, 1981),

and the Developmental Test of Visual Motor Integration (VMI) (Beery, 1989), the Comprehensive Test of Phonological Processing (CTOPP) (Wagner et al., 1999), and the Total Word Reading Efficiency test (TOWRE) (Torgesen et al., 1999).

Diffusion Tensor Imaging

Imaging was performed on a Siemens Sonata 1.5 T scanner. DTI data were obtained using a double spin echo EPI sequence with 32 directions, 1 b-value (1000s/mm²) in addition to b=0, and 1 average with TE=87, TR=6200, 128×128 acquisition matrix, Bandwidth 1630, Flip Angle 90, FOV=20×20cm, with 40 slices, 3mm thick, skip 0mm. FA values were calculated from the tensor data using BioImageSuite software (Yale University) and nonlinearly registered to a single subject FA map selected from the control group of children. Both groups of subjects were registered to this single subject template to form composite maps.

An average tensor across subjects was also computed after nonlinear registration of all subjects to a reference FA map, and the control group tensor was used to create a composite tricolor directionality map. This tricolor directionality map from the control group allows fiber bundles to be delineated according to the direction of diffusion along the fibers, and it was used to manually define anatomical regions of interest (ROIs) based on fiber bundle locations as previously described.(Constable et al., 2008) Since all of the subjects are registered in the same composite space, these ROIs were directly applied to each single subject and to group FA maps to generate individual FA values for each ROI for each subject for second level statistical analysis.

Fiber Tracking

ROIs defining the splenium of the corpus callosum and bilateral external capsules were defined using fiber tracking. We used fiber tracking on the tensor data of each subject to extract and define these regions as customized individual ROIs. Preterm subjects are well known to exhibit occipital ventriculomegaly at the time of MR imaging, and we employed this strategy for the splenium because of comparative analyses demonstrating inclusion of splenium fibers in the occipital horns of the lateral ventricles for the preterm group when ROI methods were used. Similarly, we employed fiber tracking for the external capsule so that fibers from the extreme capsule would not be included in the data set.

Volumetric analyses

To complement the DTI analyses, we employed voxel-based morphometry (VBM) to examine volume differences between the preterm and control groups.(Kesler et al., 2008) The optimized VBM process included segmentation and extraction of the brain in native space, normalization of the white matter to a standard space using a custom template created from all study subjects, segmentation and extraction of the normalized brain, modulation of the normalized white matter images to correct for tissue volume differences attributable to the normalization procedure, and smoothing using a 12-mm full width at half-maximum kernel, to reduce the effects of noise.

Statistical Methods

Demographic and cognitive data were analyzed using standard chi-squared statistics for categorical data. Continuous-valued data and ROI-based FA values were analyzed using t-tests to compare groups. General linear models (GLM) including group and gender were employed to compare volume measurements for the two groups, and volumetric data were presented as least square mean (LSM) values ± standard error of the mean (SE); GLM analyses including group, gender and total tissue volume were also used to compare FA

values for the groups. Pearson's correlations were employed to examine the relationships between FA and cognitive outcome measures, while GLM analyses were used to examine the effects of FA, total tissue volume and gender on these measures.

For the purposes of this report, p values < 0.05 were considered significant. All analyses were performed using SAS/STAT® 9.22 (SAS Institute Inc., Cary, NC).

Results

Subject population

Neonatal characteristics of the preterm population are shown in Table 1. The preterm subjects weighed between 600 and 1250 grams at birth, with a mean birth weight of 994 ± 184 grams and mean gestational age of 28.3 ± 1.9 weeks. One quarter of the subjects (26%) developed bronchopulmonary dysplasia.

Demographic data of the term and preterm cohorts are presented in Table 2. There were no significant differences between preterm and term cohorts in gender, age at scan, number of right-handed subjects, percentage of non-white subjects, subjects who receive special services or subjects whose mothers had less than a high school education.

Results of cognitive testing for the language pathway correlations are presented in Table 3. Preterm subjects scored significantly lower than term subjects on the WISC-III full scale intelligence quotient (IQ) ($p=0.003$), verbal IQ ($p=0.043$), and performance IQ ($p=0.001$). In contrast, there was no significant difference between groups in PPVT scores.

Preterm subjects performed comparably to term subjects on Non-word Repetition and Phoneme Reversal tasks, as well as Rapid Naming composite scores, which are composed of Rapid Digit Naming and Rapid Letter Naming tasks. The Phonemic Awareness Composite score, made up of tasks involving Blended Non-words and Segmented Non-words, showed significant deficits in preterm subjects compared to term ($p=0.004$). The subset tasks revealed significantly higher scores in terms than preterms in the Segmented Non-words task but no significant differences in the Blended Non-words task.

Volumetric analyses

VBM data were available for 41 preterm subjects and 41 term control subjects. Least square mean VBM analyses co-varied for gender were performed for total cerebral gray matter, total cerebral white matter and total cerebral tissue for the study groups. As shown in Table 4, preterm subjects had significantly lower values for all three VBM measures than term controls. For gray matter, there was both an effect of group ($p < 0.001$) and gender ($p < 0.001$) but no significant group-by-gender interaction ($p = 0.16$). In addition, for both groups, females had lower values than male subjects. Similarly, there was both an effect of group ($p < 0.001$) and gender ($p < 0.001$) but no group-by-gender effect for white matter volumes ($p = 0.13$) and total tissue volumes (group: $p < 0.001$; gender: $p < 0.001$; interaction: $p = 0.11$). For both white matter and total tissue volume, females had lower volumes than male subjects.

Diffusion tensor imaging analysis

Figure 1 shows orthogonal views of the ROIs representing the left arcuate fasciculus (yellow) and the left uncinate fasciculus (white), overlying a FA map of a representative control brain.

Quantitative fractional anisotropy values within a variety of regions of interest within the white matter were calculated for each cohort. Data for the language regions are presented in

Table 5. Preterm subjects had significantly lower fractional anisotropy values than term subjects in left and right uncinate fasciculi ($p = 0.01$ and 0.004 , respectively), the left and right external capsule ($p < 0.001$ for both) and the left and right inferior frontal gyri (left: $p < 0.001$; right: $p = 0.011$). Preterms also had significantly lower FA values than term subjects in the genu and splenium of the corpus callosum ($p = 0.013$ and 0.008 , respectively).

In addition, general linear model analyses were performed in which the effect of gender and total tissue volume on FA values were evaluated; results are shown in Supplemental Table 1. While the p value for the contribution of subject group (ie, preterm or term controls) to the genu of the corpus callosum increased from 0.013 (t-test) to 0.08 , no other notable changes were noted with this analysis strategy. Furthermore, there were no significant gender effects in these analyses.

Correlational analyses

Correlations between FA in specific ROIs and selected cognitive tests for the language pathways are presented in Table 6. In analyses including both term and preterm subjects there are significant positive correlations between PPVT scores and bilateral uncinate fasciculi (left: $r=0.278$, $p=0.01$; right: $r=0.278$, $p=0.01$). There were also trends for positive correlations between Rapid Naming Composite scores and bilateral arcuate fasciculi: on the left, $r=0.213$; $p=0.050$, and on the right, $r=0.208$; $p=0.056$.

Data from the preterm group alone demonstrated significant positive correlations between FA values in the left uncinate fasciculus and PPVT scores ($r=0.314$, $p=0.038$) as well as FA in the right uncinate and PPVT scores ($r=0.336$, $p=0.026$). In addition, FA values in bilateral arcuate fasciculi again show significant positive correlations with CTOPP Rapid Naming Composite scores in the preterm group (left: $r=0.424$, $p=0.004$; right: $r=0.301$, $p=0.047$). In addition, preterm subjects exhibited a negative correlation between right external capsule FA and PPVT scores ($r = -0.301$, $p = 0.047$). When analyzed in general linear models taking into account gender, age at scan, bronchopulmonary dysplasia, and birth weight, associations remained significant for preterms in bilateral arcuate fasciculi (left: R -Square= 0.337 , $p=0.005$; right: R -Square = 0.2796 , $p=0.028$) and right uncinate fasciculus (R -Square = 0.171 , $p=0.027$), with trends in the left uncinate fasciculus and the right external capsule. Graphic representations of correlations between FA values in select ROIs and scores on specific cognitive tests are presented in Figure 2.

There were no significant correlations for the term population. Positive correlations between PPVT scores and FA in left and right uncinate fasciculi did not achieve significance (left: $r=0.222$, $p=0.16$; right: $r=0.203$, $p=0.20$), while Rapid Naming Composite scores correlated poorly with FA in left and right arcuate fasciculi (left: $r=-0.135$, $p=0.40$; right: $r=0.058$, $p=0.72$). The smaller number of term subjects and lower degree of variability in FA in term subjects compared to preterm subjects may have contributed to the absence of significant correlations in this population.

There were no significant correlations for white matter volumes and either language measure for both the preterm and term control groups (data not shown; $p > 0.25$ for all).

Finally, general linear model analyses were performed in which the effect of regional FA, gender and total tissue volume on language outcome measures were evaluated; results are shown in Supplemental Table 2. While the p value for the contribution of the FA of the R arcuate fasciculus to the CTOPP Rapid Naming Composite Score for the preterm group increased slightly from 0.047 (Pearson's correlation) to 0.057 , no other notable changes were noted with this analysis strategy.

Discussion

These data support for the first time that the dual pathways underlying language function are present in prematurely-born subjects at late adolescence. Preterm subjects with no evidence of severe neonatal brain injury exhibit diffuse changes in cerebral white matter microstructure and total cerebral white matter volume compared to term controls at 16 years of age, yet our data show significant positive correlations between language measures and microstructural integrity in both the dorsal and ventral language pathways.

Within the ventral pathway, preterm adolescents showed significantly lower FA than term subjects in bilateral uncinate fasciculi, bilateral external capsules, and bilateral white matter regions subserving the inferior frontal gyrus contiguous with the uncinate fasciculi. Bilateral posterior segments of the inferior fronto-occipital fasciculus, which have also been implicated in semantic processing (Martino et al.), also showed FA deficits in preterm subjects. Increased FA in the uncinate fasciculus positively correlated bilaterally with performance on a semantic language task, the PPVT-R, consistent with previous descriptions of the ventral pathway in normally developing adults.

In contrast, the primary component of the dorsal, phonological language processing pathway, the arcuate fasciculus, showed no significant FA differences between term and preterm groups. FA in bilateral arcuate fasciculi correlated with CTOPP Rapid Naming Composite scores. This correlation between phonological task performance and bilateral dorsal pathway integrity among the preterm subjects, in contrast to the usual left-sided dominance found in populations of both adults and children (Hickok and Poeppel, 2007; Lebel and Beaulieu, 2009), implies that preterm subjects adaptively rely more heavily on the right hemisphere for performance of phonological tasks than typically developing subjects.

Deficits in FA in the preterm group were also noted in regions previously reported to be affected by premature birth, including the genu and splenium of the corpus callosum (Anderson et al., 2006; Caldu et al., 2006; Constable et al., 2008; Narberhaus et al., 2007). Although it is not included within the dual language pathways, corpus callosum disorganization may have implications for reading facility (Carreiras et al., 2009) and memory performance (Caldu et al., 2006).

The lack of correlations of FA values and testing measures for the term control subjects may be attributable to the earlier engrainment of language systems in the preterm group. Because they are at grave risk for neurodevelopmental handicap, (Woodward et al., 2009) premature infants receive special services including speech, language and early intervention from their earliest days (Milgrom et al., 2010; Spittle et al., 2010) and may experience significant improvement in language scores across developmental time periods. (Ment et al., 2003) Of note, preterm subjects at term equivalent age have been found to have higher FA values in corticospinal tracts than term controls, (Gimenez et al., 2008) likely due to the early use of those tracts. Similarly, early intervention has been shown to promote corticogenesis and improve testing scores in preclinical models for neonatal brain injury, (Faverjon et al., 2002) and also to increase FA values in preterm neonates exposed to early intervention therapy. (Als et al., 2004; Milgrom et al., 2010) Finally, our lack of correlation between FA and scores does not indicate that these tracts are not being used by the term controls but rather that the variation in their scores is attributable to other factors. Examining the dual visual streams in the developing brain, Loenneker demonstrated progressive maturation of both intra- and interhemispheric connectivity with increasing age in typically developing subjects. (Loenneker et al., 2010) Similarly, a variety of white matter tracts yet to be pruned may be used in our healthy term population to accomplish language tasks, while the preterms may have specialized earlier.

The development of sophisticated MR imaging strategies has permitted the investigation of those white matter pathways subserving language in the healthy human brain. DTI fiber tracking studies have demonstrated the dual language pathways in adult control subjects and confirm the left-ward dominance of the dorsal phonologic path connecting Broca's area, L BA44 to the left superior temporal gyrus, also known as Wernicke's area (Saur et al., 2008). Employing DTI and tractography strategies, Lebel and Beaulieu (Lebel and Beaulieu, 2009) studied the lateralization of the arcuate fasciculus in subjects ranging from ages 5 – 30 years and demonstrated that FA was significantly higher in the arcuate fasciculus in the left hemisphere compared to the right, although 10% of subjects appeared to be right-lateralized. Of note, age and gender did not appear to contribute to lateralization of this dorsal language pathway. Finally, children received cognitive assessments and were divided into three groups; a "left-only" group in which only the left arcuate could be tracked, a left-lateralized group and a right-lateralized group. In this study, scores on the NEPSY Phonological Processing task were significantly better for the left-lateralized group than the right-lateralized children.

In contrast, although task-based functional MRI and functional connectivity studies of language suggest disproportionate engagement of the right hemisphere in preterm subjects compared to term controls at school age, adolescence and young adulthood (Gozzo et al., 2009; Ment et al., 2006), microstructural studies of language are just beginning to emerge. Skranes reported decreased FA values in the external capsules and the superior, middle superior and inferior fasciculi bilaterally in 15 year old preterm subjects compared to term controls (Skranes et al., 2007). Although specific language measures were not addressed, children with low IQ had low FA values in both the external capsule and inferior and middle superior fasciculi. Similarly, our own studies of preterm subjects and term controls at age 12 years demonstrated decreases in the uncinate fasciculi bilaterally in the preterm group; FA values in the uncinate were significantly correlated with performance on a semantic task, the PPVT-R (Constable et al., 2008).

In previous studies, gender has been shown to impact preterm neurocognitive development, with preterm males at higher risk of poor outcome than preterm females (Kesler et al., 2008; Reiss et al., 2004). While our studies revealed marked gender effects at age 12 (Constable et al., 2008), few gender effects were found in our current study at age 16. Further, including gender as a covariate in general linear models associating language testing with FA did not change our results.

Limitations of our study include the sample size and the lack of advanced imaging in the neonatal period. It is probable that some of the preterm subjects had subtle white matter injury undetectable with neonatal cranial ultrasonography. In addition, we have not yet explored the impact of environmental factors, particularly level of maternal education and the impact of receiving special services. Further, the relationship between fractional anisotropy and white matter structure is still being explored; changes seen in preterm brains may be due to changes in axonal size, edema, or myelination patterns. High FA may represent structural organization which develops secondary to high levels of activity and performance within a white matter pathway; conversely, high FA may represent a necessary primary foundation for use of that pathway. Finally, unlike previous reports, (Yung et al., 2007) our data do not support a correlation between total white matter cerebral volumes and language measures, and this finding may be attributable to the age of our subjects, the testing measures examined and/or the lack of neonatal MRI data for our study subjects.

In the future, longitudinal studies including both cognitive testing and neuroimaging correlations will be helpful in confirming the sites of injury in the preterm brain and identifying biomarkers and mechanisms for recovery. The relationship between cognitive

development and white matter tracts is still poorly understood and should continue to be actively investigated. Strategies for automatic segmentation of images or development of a neonatal neuroimaging atlas will be useful to engender a common language for disparate studies of closely related neuroanatomic structures. Further, our understanding of the relationship of structure to function will be refined through the use of functional MRI, particularly resting state functional connectivity MRI.

Sixteen years after the insult of preterm birth, preterm subjects continue to show impaired performance on multiple aspects of neuropsychological testing in addition to microstructural abnormalities in diverse white matter tracts. Our data provide the first evidence that dual processing systems underlie language function in adolescents born preterm. Moreover, the bilateral correlations between phonological test performance and FA of the arcuate fasciculus in our preterm population represent a departure from the left-sided lateralization of the dorsal articulatory pathway in typically developing subjects. This suggests increased utilization of the right hemisphere in preterm subjects; future studies will explore the neurobiological basis of these results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

AIFO	Anterior inferior fronto-occipital fasciculus
CTOPP	Comprehensive test of phonologic processing
Cor Rad	Corona radiata
DTI	Diffusion tensor imaging
Ext Cap	External capsule
FA	Fractional anisotropy
FSIQ	Full scale IQ
ILF	Inferior longitudinal fasciculus
IVH	Intraventricular hemorrhage
MFG	Middle frontal gyrus
PCG	Precentral gyrus
PIFO	Posterior inferior fronto-occipital fasciculus
PIQ	Performance IQ
PT	Preterm
PPVT	Peabody Picture Vocabulary Test

ROI	Region of interest
SFOF	Superior fronto-occipital fasciculus
SLF	Superior longitudinal fasciculus
STG	Superior temporal gyrus
VBM	Voxel based morphometry
VIQ	Verbal IQ
VLBW	Very low birth weight

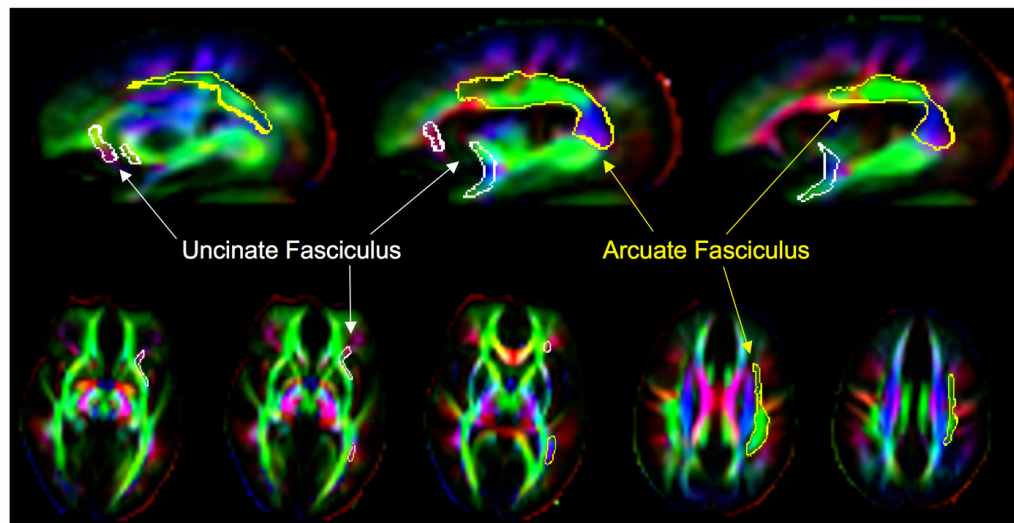
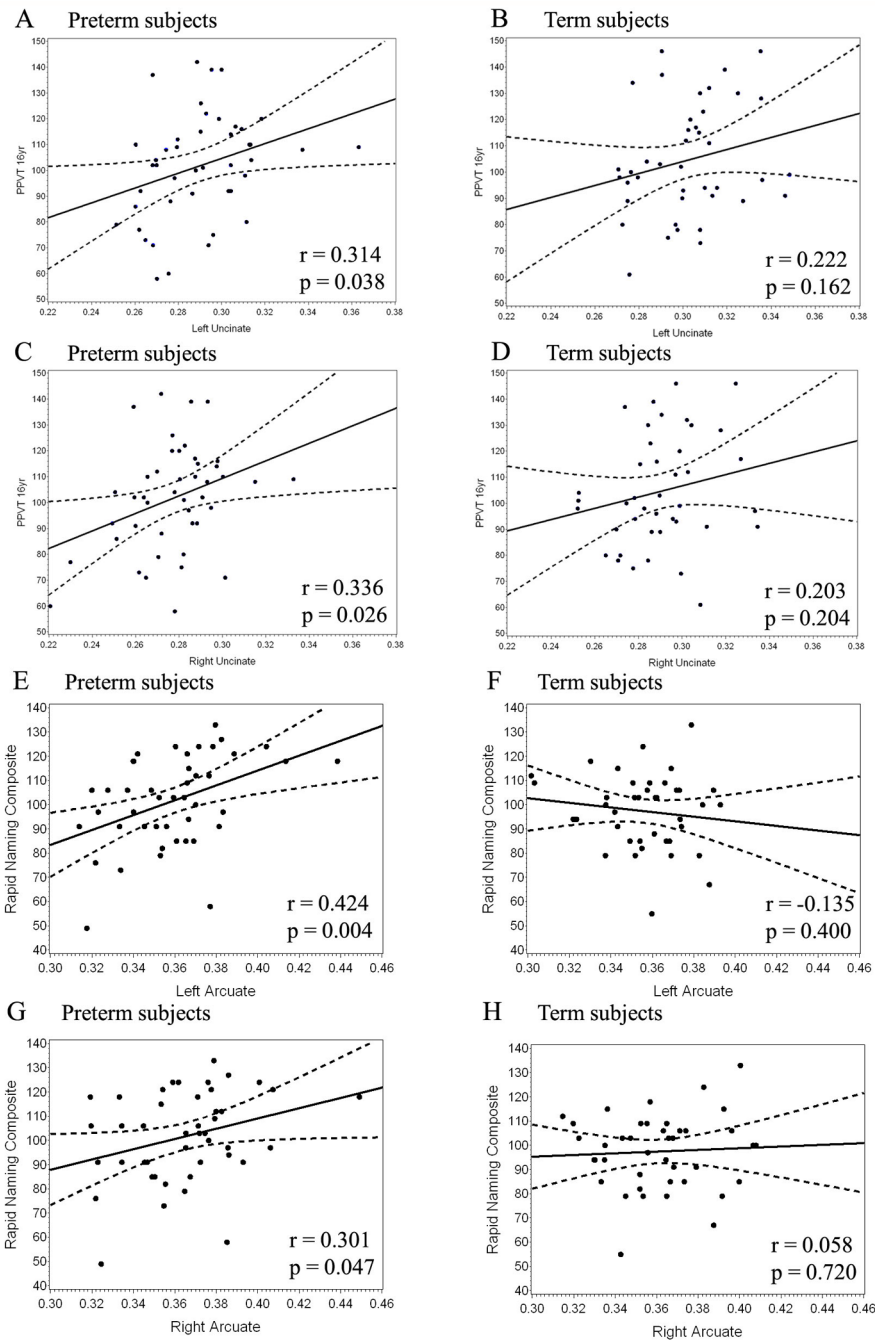


Figure 1. Tri-color fractional anisotropy maps of a control brain are presented in sagittal and axial projections. Colors represent directionality of tracts: blue indicates superior-inferior orientation, green indicates anterior-posterior, and red indicates left-right. Outlines of regions of interest overlie this map: the uncinate fasciculus in white and the arcuate fasciculus in yellow.

**Figure 2.**

Graphs show the relationship between testing scores on the y axis (PPVT in A – D; CTOPP Rapid Naming Composite scores in E – H) and FA values in specific regions on the x axis (left uncinate in A, B; right uncinate in C, D; left arcuate in E, F; right arcuate in G, H). Data are shown for preterm subjects (A, C, E, G) and term subjects (B, D, F, G) separately. The dashed lines represent 95% confidence intervals. Each black dot represents data from a single subject.

Table 1

Preterm Neonatal Data

N	44
Male, N (%)	26 (59)
Birth weight, grams, mean \pm SD	994 \pm 184
Gestational age, weeks, mean \pm SD	28.3 \pm 1.9
Bronchopulmonary dysplasia, N (%)	11 (26)
Intraventricular hemorrhage, N (%)	0 (0)
Periventricular leukomalacia, N (%)	0 (0)
Ventriculomegaly, N (%)	0 (0)

Table 2

Demographic Data for the Study Subjects

	Preterm N=44	Term N=41	p value
Male, N (%)	26 (59%)	17 (41%)	0.11
Age at scan, Years \pm SD	16.35 \pm 0.31	16.26 \pm 0.34	0.22
Right-handed, N (%)	38 (86%)	38 (95%)	0.27
Special services, N (%)	8 (18%)	4 (10%)	0.35
Non-white, N (%)	15 (34%)	14 (34%)	1.00
Maternal education less than high school, N (%)	5 (11%)	2 (5%)	0.44

Table 3

Cognitive Data

	Preterm	Term	p value
Wechsler Intelligence Scale for Children – III (WISC)			
Full Scale IQ	94.32 ± 14.25	104.56 ± 16.31	0.003
Verbal IQ	96.48 ± 15.29	103.38 ± 15.17	0.043
Performance IQ	93.14 ± 15.22	105.21 ± 17.44	0.001
Peabody Picture Vocabulary Test - Revised (PPVT)			
PPVT	101.77 ± 20.54	104.63 ± 21.39	0.53
Comprehensive Test of Phonological Processing (CTOPP)			
Rapid Naming Composite Score	101.70 ± 18.70	97.44 ± 15.32	0.26
Phonemic Awareness Composite Score	82.40 ± 13.64	91.40 ± 12.90	0.004

Table 4Volumetric data* (cm³)

	Preterm	Term	P value
Total cerebral gray	659.3 ± 7.94	700.0 ± 8.00	< 0.001
Total cerebral white	459.3 ± 6.14	494.64 ± 6.18	< 0.001
Total cerebral tissue	1118.6 ± 12.79	1194.66	< 0.001

* Least square means ± SE; data co-varied by gender

Table 5

Fractional anisotropy values for the language pathways

	Preterm	Term	p value
Longitudinal fasciculi			
Left Arcuate	0.359 ± 0.026	0.356 ± 0.022	0.46
Right Arcuate	0.365 ± 0.027	0.361 ± 0.025	0.48
Left Uncinate	0.290 ± 0.022	0.303 ± 0.021	0.01
Right Uncinate	0.278 ± 0.020	0.290 ± 0.020	0.004
External Capsule			
Left External Capsule	0.321 ± 0.017	0.347 ± 0.029	< 0.001
Right External Capsule	0.327 ± 0.024	0.346 ± 0.025	< 0.001
Corpus Callosum			
Genu	0.536 ± 0.059	0.565 ± 0.045	0.013
Body	0.484 ± 0.060	0.500 ± 0.043	0.15
Splenium	0.668 ± 0.055	0.694 ± 0.034	0.008
Subcortical White Matter Regions			
Left Inferior Frontal Gyrus	0.247 ± 0.022	0.268 ± 0.025	< 0.001
Right Inferior Frontal Gyrus	0.248 ± 0.025	0.262 ± 0.022	0.011

All FA values are presented as mean value ± SD

Table 6

Pearson correlations

Test	Region	All subjects		Preterm		Term	
		r	p value	r	p value	R	p value
PPVT	L uncinata	0.2782	0.01	0.3143	0.038	0.2223	0.16
	R uncinata	0.2781	0.01	0.3358	0.026	0.2026	0.20
	L external capsule	-0.0240	0.83	-0.1901	0.22	0.0011	0.99
	R external capsule	-0.1270	0.25	-0.3013	0.047	-0.0273	0.87
CTOPP Rapid Naming Composite Score	L arcuate	0.2132	0.050	0.4238	0.004	-0.1349	0.40
	R arcuate	0.2077	0.056	0.3010	0.047	0.0578	0.72

PPVT: Peabody Picture Vocabulary Test. CTOPP: Comprehensive Test of Phonological Processing. L: left. R: right.