8-17-2010

PRETERM BIRTH RESULTS IN ALTERATIONS IN NEURAL CONNECTIVITY AT AGE 16 YEARS

Katherine Mullen

PRETERM BIRTH RESULTS IN ALTERATIONS IN NEURAL CONNECTIVITY AT AGE 16 YEARS

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

Katherine Marie Mullen

2010

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

Katherine M. Mullen[1,2], Betty R. Vohr[3], Karol H. Katz[1,4], Karen C. Schneider[3], Cheryl Lacadie[2], Michelle Hampson[2], R. Todd Constable[2] and Laura R. Ment[1,5].

[1]Pediatrics, Yale School of Medicine, New Haven, CT, United States; [2]Diagnostic Radiology, Yale University, New Haven, CT, United States; [3]Pediatrics, Warren Alpert Medical School of Brown University, Providence, RI, United States;; [4]Epidemiology and Public Health, Yale School of Medicine, New Haven, CT, United States and [5]Neurology, Yale School of Medicine, New Haven, CT, United States.

Very low birth weight preterm (PT) children are at high risk for brain injury. This study investigates microstructural differences in the brains of PT adolescents relative to term control subjects using diffusion tensor imaging (DTI), as well as studying their neurodevelopmental outcomes. 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 ($p = 0.002$), verbal ($p = 0.027$), and performance IQ tests ($p = 0.001$), as well as CTOPP phonological awareness ($p = 0.005$), but scored comparably to term subjects on PPVT and CTOPP Rapid Naming tests. PT subjects had lower fractional anisotropy (FA) values, suggestive of white matter disorganization, in multiple regions including bilateral uncinate fasciculi (left: $p = 0.004$; right: $p = 0.002$), bilateral external capsules (left: $p < 0.0001$; right: $p = 0.001$), the splenium of the corpus callosum ($p = 0.014$), and white matter serving the inferior frontal gyrus bilaterally (left: $p < 0.0001$; right: $p = 0.005$). 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 the recently proposed concept of dual pathways underlying language function are present in PT adolescents. These include a left-sided dorsal pathway associated with phonological and articulatory processing (arcuate fasciculus), and a bilateral ventral pathway for semantic, receptive language processing (uncinate fasciculus). The striking bilateral dorsal correlations for the PT group suggest that prematurely born subjects rely more heavily on the right hemisphere than typically developing adolescents 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.

Acknowledgements

This work was supported by NS 27116 and NCRR CTSA-T32 Medical Student Research Fellowship from the National Institutes of Health.

I am greatly appreciative to my mentors, Dr. Laura Ment and Dr. Todd Constable, for the opportunity to work on this project and for their support and help in its completion.

I would also like to thank all those whose support enabled me to finish this thesis, particularly my friends for their cheer and my family for their love. Above all, I am deeply grateful to Dave Gorin, whose love and friendship humbles me and makes all worthwhile.

Table of Contents

Introduction

Consequences of preterm birth in the brain

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 (1). Premature infants suffer a high risk of perinatal brain damage compared to term infants (2-4). Though survival of infants weighing 501-1500 grams at birth has increased to 85% (5), these children face a range of developmental disabilities ranging from cerebral palsy to learning disabilities (4, 6). The brains of infants born prematurely face both increased challenge and increased susceptibility to a number of factors resulting in brain injury and secondary disturbance of growth. Active migration, axonal growth, proliferation and maturation of oligodendrocytes, and development of synaptic connections typically occur during the third trimester of fetal development, and all may be disrupted by premature birth.

Severe brain injuries such as intraventricular hemorrhage, periventricular hemorrhagic infarction, and ventricular dilatation are recognized as potentially devastating complications of preterm birth. Apart from these three catastrophic but rare complications, preterm neonates may suffer a characteristic pattern of brain injury known as encephalopathy of prematurity (7). Typically, these infants suffer injury to cerebral white matter known as periventricular leukomalacia (PVL). PVL has multiple forms, and may include either localized or diffuse changes. The pathology of localized PVL is characterized by necrosis of all cell types on a microscopic or macroscopic scale. Macroscopic foci of necrosis lead to cystic structures observable by ultrasound, leading to the characterization of this subgroup as “cystic PVL”, which is the subtype most likely

to result in severe developmental abnormalities such as cerebral palsy (7). Non-cystic PVL, on the other hand, is characterized by microscopic necrotic foci, which lead to nonspecific glial scars which may not be detected by ultrasound.

Preterm birth damages the development of the brain through multiple mechanisms. Ischemia and inflammation are initiating factors which potentiate each other, with excitotoxicity and free-radical attack as downstream effectors of this damage. Pathological correlates of diffuse injury include the disruption of premyelinating oligodendrocytes, which are particularly susceptible to injury, with subsequent reactive proliferation of oligodendrocyte precursors which unfortunately have impaired ability to myelinate axons (7). There is evidence in an animal model that the pattern of injury in preterm birth may be influenced by the distribution of immature oligodendrocytes in the brain (8, 9). In addition to glial disruption, diffuse disruption of axons has been reported in the brains of preterm infants (10). Deep gray matter is also commonly affected, including the thalamus, basal ganglia, and cerebellum, though it is unknown whether this is a primary injury or secondary trophic disturbance (7).

Investigation of the neuropathology of preterm birth has utilized post-mortem pathological analysis and study of animal models of prematurity, including subjecting animals to hypoxia, hypoxia in conjunction with ischemia through ligation of the carotid artery, or premature delivery (11). However, neuroimaging of premature infants presents a vital non-invasive method for studying changes within the still-developing brain.

Longterm effects of preterm birth on cognitive ability

In addition to feared neurological complications of preterm birth such as cerebral palsy, a range of developmental deficits in cognitive and motor function in preterm children have been observed to persist until early adulthood, indicating long-term disruption of brain function (6, 12). Preterm children have the greatest risk of neurodevelopmental deficits with severe brain injury such as intraventricular hemorrhage, periventricular hemorrhagic infarction, periventricular leukomalacia, or severe ventriculomegaly; however, even preterm children without these forms of brain injury are more likely than control term children to have lower IQ scores and require more support in reading, writing, and mathematics (13) at 12 years of age. Male infants are at particular risk for poor outcome after premature birth (14-17). The mechanism for these differences is as yet unknown.

Despite the prevalence of these difficulties, the brains of infants and children exhibit remarkable plasticity, and many catch up over time to children born at term in terms of both developmental and neuroimaging parameters (18, 19). Some studies have proposed that this compensation relates to utilization of alternative pathways in order to bypass injured white matter structures (20-22).

Neuroimaging and principles of diffusion tensor imaging

Multiple neuroimaging techniques have been used to better identify and describe the sequelae of preterm birth in the brains of these infants (23-25). While ultrasound and computed tomography have been used for some time in the identification of intraventricular hemorrhage and periventricular leukomalacia, the advent of magnetic resonance imaging (MRI) became crucial to identifying more subtle changes in the brains

of preterm infants (26). Subtle changes such as delays in gray-white differentiation, hyperintensity of white matter, smaller corpus callosum, and ventriculomegaly were appreciated with much greater sensitivity with MRI (2, 27). Methods such as voxel-based morphometry, providing volumetric analysis of white and gray matter in the developing brain, have identified relative decreases in volume of widespread white matter regions in preterm infants, suggestive of neuronal loss (15, 28-31).

Diffusion tensor imaging (DTI) is a relatively recent magnetic resonance imaging technique which provides a means of assessing the integrity of white matter tracts at a microstructural level. It is more sensitive than conventional magnetic resonance imaging for detecting subtle abnormalities (32-38). As part of DTI analyses, fractional anisotropy (FA) values indicate 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 serve as 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 flow. Alterations in FA may result from changes in fiber organization, axonal size (39), or activity-dependent changes in myelination (18). DTI has become a valuable tool in assessing white matter integrity on a microstructural level in the developing preterm brain (40-42).

FA values in white matter tracts tend to increase both over the course of fetal development and after birth. DTI conducted on fetuses *in utero* confirms increases in FA as the fetuses progress closer to term, particularly in the corticospinal tract and corpus callosum (43).FA values in multiple white matter tracts including the splenium and

posterior body of the corpus callosum, the posterior limb of the internal capsule, the left frontal white matter, and the left inferior longitudinal white matter at term equivalent age demonstrate a linear correlation with gestational age at birth (44).

Lower birthweight has also been associated with lower FA values. FA values in the corpus callosum at 11 years of age have been shown to be correlated with birthweight (45). Indeed, in studies of healthy infants born between 34 and 41 weeks gestation, FA values are higher in subcortical white matter tracts such as the corticospinal tract, callosal radiations, and thalamic radiations in infants born closer to term (46).

One study has suggested that this increase in FA in early development may be accelerated by preterm birth, as evidenced by higher FA values in preterm infants at term equivalent than in control term infants; this difference is hypothesized to be due to the increased stimulation associated with premature birth (47). The implications of this intriguing finding for later development have not been fully explored; studies comparing FA in older preterm children and adolescents to term controls have more commonly found lower FA values in the preterm subjects, as will be discussed later.

In addition to the insult of prematurity, multiple other confounding factors may impact FA values and brain development in these infants. Independent of factors including age at scan and degree of prematurity, lung disease has been shown to be associated with white matter abnormalities in preterm children (44). In this study using tract-based spatial statistics, a method based in DTI data, infants with greater than two days of mechanical ventilation showed reduced FA in the genu of the corpus callosum at term equivalent age, and infants who developed chronic lung disease showed reduced FA in the left inferior longitudinal fasciculus (44). In addition, postnatal infections and

hypotension have also been indicated to confer an increased risk of white matter injury, as measured by lower FA on DTI and lower N-acetylaspartate/choline on MR spectroscopy (48).

Brain areas found to be affected by preterm birth

Multiple previous studies have shown deficits in FA values in white matter tracts in premature infants at term-equivalent age as compared to term infants (41, 42, 44, 47, 49-55). For example, in a study using tract-based spatial statistics, a DTI-based method, reductions in FA were founds in term-equivalent preterm infants in regions including the centrum semiovale, frontal white matter, and genu of the corpus callosum (52). In this study, infants born at 28 weeks of gestation or less were found to have lower FA in the external capsule and portions of the posterior limb of the internal capsule and body of the corpus callosum than infants born at greater gestational ages (52).

Studies have also been conducted to study changes in neuroimaging parameters persisting to late childhood and adolescence (14, 29, 30, 56-63). Lower FA values in the external capsules, posterior corpus callosum, and fornix have also been reported in adolescents born preterm (64), and in the internal and external capsule, corpus callosum, and superior, middle superior, and inferior fasciculi of 15 year olds born with very low birthweight (60). In a study of 12 year old children born preterm (30), multiple areas of decreased FA were found in preterm children compared to term children, including bilateral anterior portions of the uncinate fasciculi, the splenium of the corpus callosum, and the right inferior fronto-occipital fasciculus.

The relationship between FA and developmental outcome, however, is complex; not all studies demonstrate globally lower FA values in preterm children than term children. For example, significantly higher FA values were found in the corticospinal tracts of preterm infants at term equivalent age than term controls, though within the same cohort FA values were reduced in the splenium of the corpus callosum in the preterm group (54). This may represent a rearrangement of white matter tracts compensating for white matter injury in preterm infants, effects of differences in water concentration, or the presence of crossing fibers, and calls attention to the complex tissue properties that may affect FA values.

Neurodevelopmental testing correlates with FA values

FA values have been shown to correlate with performance on multiple measures of neurodevelopmental function (18, 60, 65-72). In school age preterm children, whole-brain FA was an independent variable affecting full scale IQ after adjusting for birthweight, gestational age, and gender (59). Other studies have correlated cognitive scores with FA in specific regions of the brain. DTI of low birthweight preterm infants showed lower FA values in the posterior limb of the internal capsule in infants with cerebral palsy or other neurological deficits compared to neurologically intact infants (67, 70). In older children (mean 5 years of age), those with cerebral palsy also showed lower FA in thalamocortical radiations, correlating with reduced contralateral touch threshold, proprioception, and motor deficits (73).

DTI data has also been used to correlate FA values in the optic radiations, defined using probabilistic diffusion tractography (71) or quantitative fiber tracking analysis (72), with measures of visual function at term equivalent age (71) or earlier (72).

Preterm children studied with DTI and the Griffiths Mental Development Scale at 2 years of corrected age showed linear relations of developmental quotient to FA values in the corpus callosum and right cingulum, correlations between performance sub-scores and the corpus callosum and right cingulum, and correlations between eye-hand coordination scores to FA in the cingulum, fornix, anterior commissure, corpus callosum, and right uncinate fasciculus (61).

Reading performance scores have been found to positively correlate with FA values in the genu and body of the corpus callosum in a group of 11 year old preterm children (45). In 12 year old children born preterm, correlations were found between the left anterior uncinate fasciculus with WISC verbal IQ and full scale IQ, in addition to PPVT scores (30). In adolescents at 15 years of age with birthweight less than 1500 grams, correlations were found between low IQ and low FA in the external capsule and inferior and middle superior fasciculus, as well as between low FA in the external capsule, posterior internal capsule, and inferior fasciculus with visual motor and visual perceptual deficits (60). In a cohort of young adults born preterm, increases in mean diffusivity in the genu of the corpus callosum were correlated with lower performance IQ (63).

Multiple studies, therefore, indicate a link between DTI/FA findings in the preterm brain and neurodevelopmental and cognitive outcome. It is important to note, however, that statements of causation cannot be made. It is not clear whether changes in

white matter microstructure, as measured by differences in FA in specific pathways, are the cause or the result of poor test performance.

Language processing: lateralization and the dual pathway system

Understanding of the brain structures underlying language function has become more complex since initial pathologic-deficit correlations identifying Wernicke's area, important for semantically appropriate language comprehension and production, and Broca's area, important for production of speech sounds. Recent investigations have proposed dual systems of language processing, analogous to dual pathways identified in visual processing (74-76). In the visual system, a ventral pathway carries "what" information for object recognition, and a dorsal pathway carries "how" information for spatial and sensorimotor processing. In the language processing 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.

Further studies have studied the white matter tract correlates of these theoretical pathways. Each pathway involves fibers traveling from the superior temporal gyrus. The superior longitudinal fasciculus (arcuate fasciculus) has been identified as the primary component of the dorsal pathway, while the ventral pathways are likely comprised of fibers traveling through the extreme capsule (76). The uncinate fasciculus, a ventral pathway connecting the temporal and frontal lobes which runs close to the projected ventral pathway through the extreme capsule, has also been implicated in language

processing (77, 78). The ventral pathway is thought to be bilateral, while the dorsal pathway tends to be strongly left-dominant (74, 77).

Of note, the above investigations of the dual pathway language systems have taken place in adult subjects. In fact, in young children (5 years of age), there appears to be less specialization of semantic vs. syntactic tasks than in adults (79). Though the developmental timing of specialization of these pathways is not fully understood, fMRI studies in older children (10-12 years of age) have described differential patterns of activation in response to semantic and phonologic tasks (21, 81-82). These studies have not yet elucidated the white matter correlates of this functional separation in developing children.

Further, preterm children may develop language pathways differently than normally developing term children (78). In an fMRI task analyzing passive listening to language, children born preterm were shown to preferentially engage areas involved in phonological processing, while children born at term were more likely to activate semantic processing systems (21, 80). Functional connectivity analyses performed with fMRI techniques 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 (78).

Summary

In summary, children born preterm are at significant risk of brain injury and developmental disability. Neuroimaging measures such as DTI are valuable in investigating microstructural changes in the preterm brain, and in multiple previous

studies have shown longstanding alterations in white matter microstructure in preterm children correlating with cognitive and developmental performance. For language tasks in particular, preterm children may engage alternative pathways, including increased utilization of the right hemisphere. These findings may represent a delay in maturation compared to term control subjects – or they may be employed by the preterm group to compensate underlying changes in glio- and/or neurogenesis.

Statement of Purpose

Overall, this project will examine the long-term impact of preterm birth on neural connectivity, using DTI data as an indicator of the microstructural integrity of white matter tracts and cognitive testing from preterm and term 16 year old subjects.

First, FA values in a variety of regions of interest will be statistically compared by group and gender. We hypothesize that FA values will be lower in preterm than term children at 16 years of age, indicating more disorganization of white matter tracts, in regions such as the uncinate fasciculus, which is the major ventral pathway involved in semantic language processing. Since previous studies have found differences in male and female subsets, we hypothesize that gender will influence differences between preterm and term adolescents.

Second, we will statistically compare cognitive testing scores, taking group and gender into account. We hypothesize that preterm children will suffer deficits in cognitive scores, particularly on verbal testing, compared to term children.

Finally, we hypothesize that scores on language subsets of cognitive tests will positively correlate with FA values in white matter regions known to be important in language processing, such as the arcuate and uncinate fasciculi. We further hypothesize that these correlations will exist in both hemispheres of preterm children, given previous fMRI research showing activation of bilateral language networks in preterm children (78).

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 and analyzed at Yale 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 neurologic findings and total ventricular CSF volume within 2 SD of the mean ventricular volume of term control subjects at 12 years of age and no contraindications to MRI. All preterm subjects enrolled in the follow-up component of the "Multicenter Randomized Indomethacin IVH Prevention Trial" (83, 84) 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 from which they were selected 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 group by age, sex and minority status.

The assessments of neonatal health status and neurologic outcome have been previously described (66). Blinded assessment of intelligence was performed using the Wechsler Intelligence Scale for Children-III (WISC) (85). Children also received the

Peabody Picture Vocabulary Test –Revised (PPVT), and the Developmental Test of Visual Motor Integration (VMI), the Comprehensive Test of Phonological Processing (CTOPP), and the Total Word Reading Efficiency test (TOWRE).

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 values (1000s/mm2) and 1 average with TE=87, TR=6200, 128x128 acquisition matrix, Bandwidth 1630, Flip Angle 90, FOV=20x20cm, with 40 slices, 3mm thick, skip 0mm. Thirty-two separate acquisitions were averaged and the diffusion tensor computed from these data. FA values were calculated by KM 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 by KM to this single subject template to form composite maps.

An average tensor across subjects was also computed by KM 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 by KM to manually define anatomical regions of interest (ROIs) based on fiber bundle location with reference to a previously published DTI atlas of white matter tracts(86). Since all of the subjects are registered in the same composite space, these ROIs were directly applied by KM 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.

Statistical Methods

Demographic and cognitive data were analyzed using standard chi-squared statistics for categorical data. Continuous-valued data were analyzed using analysis of covariance (ANCOVA) including the terms group, gender, and group-by-gender interaction. For the DTI data, the ROI-based FA values were entered into an ANCOVA model to examine main effects of group and gender, and an interaction term for group-by-gender. General Linear Models were used for evaluating associations between selected cognitive scores and FA in specific ROIs adjusting for prognostic factors.

Results

Table 1. Neonatal data

Neonatal characteristics of the preterm population are shown in Table 1. The included preterm subjects weighed between 600 and 1250 grams at birth, with an average birthweight of 994 grams ± 184 grams. The average gestational age of preterm subjects was 28.3 weeks ± 1.9 weeks. No subjects had evidence of intraventricular hemorrhage, periventricular leukomalacia, or ventriculomegaly by ultrasound as neonates. One quarter of the subjects (26%) developed bronchopulmonary dysplasia.

Table 1

Neonatal Data for Preterm Subjects

	Preterm
N	44
Male, N (%)	26 (59%)
Birthweight, mean ± SD, grams	994 ± 184
Gestational Age, mean ± SD, weeks	28.3 ± 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

Demographic data of the term and preterm cohorts is presented in Table 2. Notably, there was a higher percentage of male subjects in the preterm cohort (59%) than in the term cohort (41%). There was no significant difference in the preterm and term cohorts in age at scan.

There was a trend for higher weight in males than females among both preterm and term groups, with no difference between preterm and term cohorts. There was a significant gender effect on height, with males taller than females in both preterm and term groups. In addition, there was a significant group by gender interaction in height ($p=0.0320$), such that preterm males were slightly taller than term males (170.4 ± 9.2 cm vs. 169.2 ± 9.8 cm) while preterm females on average lagged notably behind term females (156.0 ± 9.9 cm vs. 163.3 ± 5.6 cm).

Among the preterm subjects, 92% of males and 78% of females were right-handed, while 88% of male term subjects and 100% of female term subjects were right-handed, but these differences did not show significant group or gender effects.

There were no significant differences in percentage of non-white subjects or percentage of subjects who had received special services as children.

There was a trend for higher levels of maternal education in the term cohort compared to the preterm cohort. While the mothers of preterm male and female subjects had respectively 13.2 ± 2.2 and 13.4 ± 2.2 years of education, the mothers of term male and female subjects had 14.1 ± 3.0 and 14.8 ± 2.9 years of education respectively. There was not a significant gender interaction. There were not a significantly different number of mothers with less than a high school education in the preterm or term cohorts.

Table 2

Demographic Data							
	Preterm		Term		P value		
	Male	Female	Male	Female	Group	Gender	Interaction
N	26	18	17	24			
Age at scan, mean ± SD, years	16.4 ± 0.4	16.3 ± 0.2	16.2 ± 0.3	16.3 ± 0.3	0.2416	0.8921	0.1557
Height, mean ± SD, cm	170.4 ± 9.3	156.0 ± 9.9	169.2 ± 9.8	163.3 ± 5.6	0.1170	**<0.0001**	**0.0320**
Weight, mean ± SD, kg	71.1 ± 19.2	65.6 ± 17.9	73.4 ± 17.1	65.2 ± 15.0	0.8060	0.0859	0.7366
Right-handed (N, %)	24 (92%)	14 (78%)	14 (88%)	24 (100%)	0.2694	1.0000	0.7940
Special services (N, %)	5 (19%)	3 (17%)	3 (18%)	1 (5%)	0.8962	0.1850	0.3264
Nonwhite (N, %)	9 (35%)	6 (33%)	5 (29%)	9 (38%)	0.7221	0.5913	0.6532
Maternal Education, mean ± SD, years	13.2 ± 2.2	13.4 ± 2.2	14.1 ± 3.0	14.8 ± 2.9	0.0503	0.4194	0.6623
Maternal Education less than high school (N, %)	2 (8%)	3 (17%)	1 (6%)	1 (4%)	0.8203	0.8026	0.4780

Table 3. Cognitive testing data by group and gender

Results of cognitive testing of all 16 year old subjects are presented in Table 3, including Wechsler Intelligence Scale for Children-III (WISC-III), Peabody Picture Vocabulary Test- Revised (PPVT-R), Visual Motor Integration (VMI), Comprehensive Test of Phonological Processing (CTOPP), and Test of Word Reading Efficiency (TOWRE).

For the WISC-III full scale intelligence quotient (IQ), male preterm subjects on average scored 95.3 ± 12.6 and female preterm subjects scored 92.9 ± 16.6, while male term subjects on average scored 107.7 ± 15.6 and female term subjects scored 102.4 ±16.8. There was a significant difference between term and preterm cohorts (p=0.0020).

The WISC-III Verbal IQ testing showed that male preterm subjects scored on average 98.5 ± 14.7, and female preterms scored 93.6 ± 16.1, while male term subjects on average scored 105.6 ± 15.1 and female term subjects scored 101.8 ± 15.4. This represented a significant difference between preterm and term groups (p=0.0269).

The WISC-III Verbal Comprehension IQ testing showed a trend for differences between the groups (p=0.0587), with average scores of 99.2 ± 14.4 in male preterms, 95.6 ± 16.7 in female preterms, 104.7 ± 13.5 in male terms, and 103.2 ± 16.0 in female terms.

The WISC-III Performance IQ statistics demonstrate significant group differences between term and preterm subjects, with subjects achieving average scores of 92.9 ± 14.9 for male preterms, 93.4 ± 16.1 for female preterms, 108.8 ± 15.8 for male terms, and 102.7 ± 18.4 for female terms.

Table 3

Cognitive Data							
	Preterm		Term		P value		
	Male	Female	Male	Female	Group	Gender	Interaction
Wechsler Intelligence Scale for Children – III (WISC)							
Full Scale IQ	95.3 ± 12.6	92.9 ± 16.6	107.7 ± 15.6	102.4 ± 16.8	**0.0020**	0.2630	0.6753
Verbal IQ	98.5 ± 14.7	93.6 ± 16.1	105.6 ± 15.1	101.8 ± 15.4	**0.0269**	0.2040	0.8672
Verbal Comprehension IQ	99.2 ± 14.4	95.6 ± 16.7	104.7 ± 13.5	103.2 ± 16.0	0.0587	0.4564	0.7621
Performance IQ	92.9 ± 14.9	93.4 ± 16.1	108.8 ± 15.8	102.7 ± 18.4	**0.0010**	0.4556	0.3749
Peabody Picture Vocabulary Test - Revised (PPVT)							
PPVT	103.7 ± 19.3	99.0 ± 22.4	108.0 ± 19.2	102.3 ± 22.9	0.4179	0.2639	0.9096
Developmental Test of Visual Motor Integration (VMI)							
VMI	78.8 ± 13.8	75.9 ± 11.1	89.8 ± 11.7	83.2 ± 12.9	**0.0015**	0.0935	0.4975

Table 3 (continued)

Cognitive Data							
	Preterm		Term		P value		
	Male	Female	Male	Female	Group	Gender	Interaction
Comprehensive Test of Phonological Processing (CTOPP)							
16yr Rapid Digit Naming	9.3 ± 2.8	11.3 ± 2.7	9.7 ± 3.3	9.2 ± 2.1	0.1424	0.2149	**0.0402**
16yr Rapid Letter Naming	10.0 ± 3.8	10.9 ± 3.5	9.7 ± 3.7	9.8 ± 1.9	0.2917	0.5109	0.5508
Rapid Naming Composite	98.2 ± 19.0	106.8 ± 17.5	98.2 ± 20.2	96.9 ± 11.1	0.1933	0.3339	0.1861
16yr Nonword Repetition	8.2 ± 1.9	9.1 ± 2.4	9.2 ± 2.2	8.7 ± 1.9	0.4564	0.7217	0.1366
Phoneme Reversal	8.1 ± 2.4	8.6 ± 2.5	9.7 ± 2.9	8.4 ± 2.2	0.2059	0.5006	0.1228
Blend NonWords	7.9 ± 2.3	8.9 ± 3.2	9.6 ± 3.0	9.2 ± 1.7	0.0836	0.6060	0.2486
Segmented Nonwords	5.8 ± 2.3	6.0 ± 3.0	8.3 ± 2.5	7.4 ± 2.4	**0.0014**	0.5418	0.3300
Phonemic Awareness Composite	81.0 ± 11.3	84.6 ± 16.8	93.8 ± 15.9	89.8 ± 10.7	**0.0051**	0.9580	0.2270
Total Word Reading Efficiency (TOWRE)							
16yr Total Word Reading Efficiency	89.2 ± 11.3	95.4 ± 11.8	93.4 ± 16.1	96.1 ± 13.6	0.3913	0.1264	0.5450

There were no significant differences between groups or genders in PPVT scores; averages in male and female preterm and term groups ranged between 99 and 108 with standard deviations of 19 to 22.

Preterm subjects on average scored significantly lower than term subjects on VMI testing ($p=0.0015$), and there was a trend for male subjects scoring better than female subjects ($p=0.0935$). Preterm males scored on average 78.8 ± 13.8 on this test, while preterm females scored 75.9 ± 11.1; meanwhile, term males scored 89.8 ± 11.7 and term females scored 83.2 ± 12.9.

While some subsets of CTOPP testing revealed differences between term and preterm cohorts, other scores were indistinguishable. Rapid Naming composite scores, which are composed of Rapid Digit Naming and Rapid Letter Naming tasks, revealed no significant differences between the groups. Within the Rapid Digit Naming subset, however, there was a significant group-by-gender effect ($p=0.0402$) such that preterm females scored higher than preterm males (11.3 ± 2.7 vs. 9.3 ± 2.8), while term males scored higher than preterm females (9.7 ± 3.3 vs. 9.2 ± 2.1). Preterm subjects also performed comparably to term subjects on Non-word Repetition and Phoneme Reversal tasks. The Phonemic Awareness Composite score, made up of tasks involving Blended Non-words and Segmented Non-words, showed a significant difference ($p=0.0051$) between term and preterm cohorts. While preterm males achieved an average score of 81.0 ± 11.3 and preterm females scored 84.6 ± 16.8, term males scored 93.8 ± 15.9 and term females scored 89.8 ± 10.7. The subsets revealed significantly higher scores in terms than preterms in the Segmented Non-words task but no significant differences in the Blended Non-words task.

TOWRE 16 year old standard scores revealed no significant differences among the term and preterm cohorts.

Figure 1. Mapping regions of interest

Axial slices through a representative diffusion tensor image of a control brain, showing directional fractional anisotropy values, are shown in Figure 1A. Red represents left-right orientation of fibers, blue represents superior-inferior orientation of fibers, and green represents anterior-posterior orientation of fibers. Greater intensity of color represents higher values of fractional anisotropy. In Figures 1B-1C, representative ROIs are shown in blue overlying a grayscale fractional anisotropy map of a control brain, in which high levels of FA are white and low FA regions are black. Figure 1B shows the mapped region of the left arcuate fasciculus in blue in sagittal, coronal, and axial projections over a control brain. Figure 1C shows the left uncinate fasciculus in blue in sagittal, coronal, and axial planes over a control brain.

Figure 1

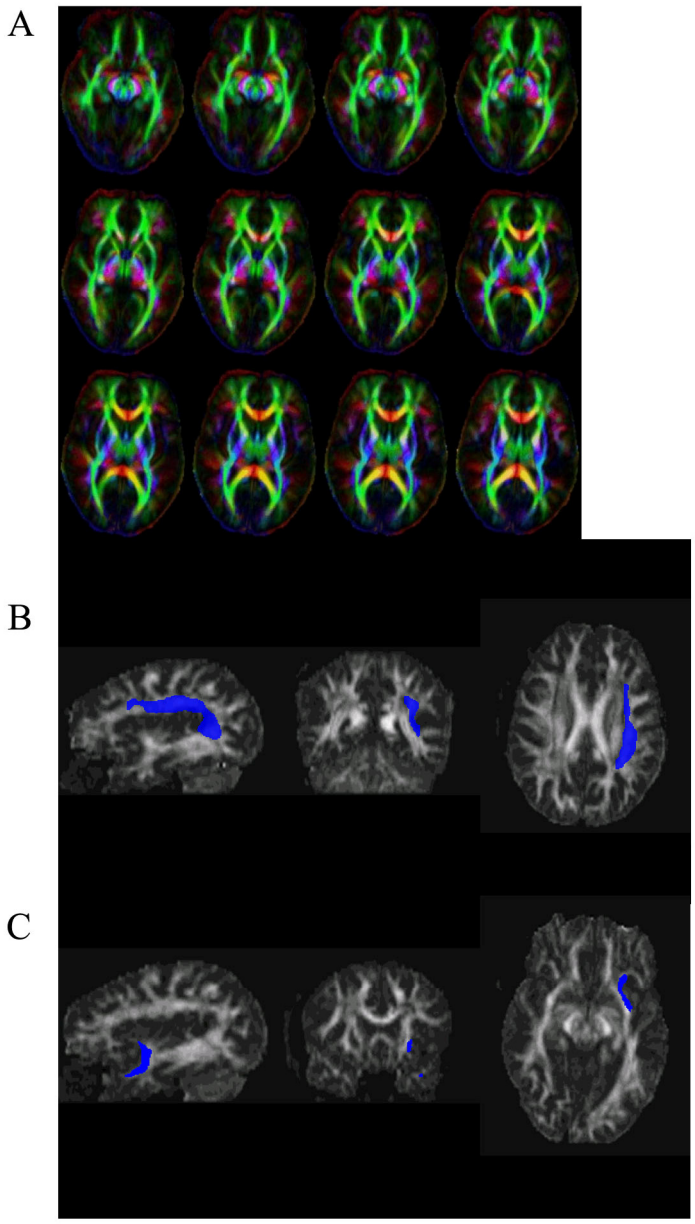

Figure 1.

Figure 1A shows multiple axial slices through a composite tridirectional fractional anisotropy (FA) map. Fiber directions are coded as follows: red, left-right; blue, superior-inferior; green, anterior-posterior. Figures 1B and 1C show sagittal, coronal, and axial grayscale FA maps with regions of interest mapped in blue (1B: arcuate fasciculus; 1C: uncinate fasciculus).

Table 4. Fractional anisotropy in regions of interest by group and gender

Quantitative fractional anisotropy values were obtained in each brain within a variety of regions of interest representing white matter tracts, and statistics regarding effects of group and gender were calculated for each cohort.

No significant differences were seen within the groups for multiple regions of interest, including left and right arcuate fasciculi, left and right AIFOF, left and right SFOF, left and right ILF, posterior limbs of the left and right internal capsules, left and right cingulum, left and right fornices, and left and right forceps major.

Term subjects had significantly higher fractional anisotropy values than preterm subjects in left and right PIFOF regions ($p=0.0037$ and $p=0.0135$ respectively). In addition, there was a trend in the left PIFOF for a gender effect ($p=0.0638$) and a significant group-by-gender interaction ($p=0.0183$), with lower fractional anisotropy values in male preterm subjects (0.395 ± 0.03) compared to female preterm subjects (0.418 ± 0.02), while male and female term subjects had very similar values (0.423 ± 0.02 vs. 0.421 ± 0.02).

The left and right uncinate fasciculi each had significantly higher FA values in the term group than the preterm group (left: $p=0.0042$, right: $p=0.002$), and there was a trend for an effect of gender in the left uncinate fasciculus ($p=0.0639$) such that males had higher FA values than females. In the left uncinate fasciculus, male and female preterms had FA values of 0.292 ± 0.02 and 0.288 ± 0.02 respectively, while male and female terms had respective FA values of 0.311 ± 0.02 and 0.297 ± 0.02. In the right uncinate fasciculus, male and female preterm subjects had FA values of 0.278 ± 0.02 and $0.277 \pm$

0.01 respectively, while male and female term subjects had FA values of 0.298 ± 0.02 and 0.285 ± 0.02 respectively.

In the corpus callosum, there was a significant effect of gender in the genu ($p=0.0377$) and a trend in the body ($p=0.0573$) such that females had higher FA values in both term and preterm cohorts. In the splenium there was not a notable effect of gender, but the preterm group (male: 0.664 ± 0.05 and female: 0.672 ± 0.06) had significantly lower FA values than the term group (male 0.692 ± 0.04 and female 0.696 ± 0.03), with $p=0.0140$.

The anterior limb of the left internal capsule demonstrated a significant effect of gender ($p=0.0219$) such that male had higher FA values than females (0.397 ± 0.02 vs. 0.394 ± 0.02 in the preterm group, and 0.413 ± 0.02 vs. 0.394 ± 0.02 in the term cohort). These values showed trends for effects of group ($p=0.0623$) and group by gender ($p=0.0842$). There were no significant effects in the anterior limb of the right internal capsule.

Preterm children on average had significantly lower FA values in both left and right external capsules than term children ($p<0.0001$ and $p=0.0007$ respectively). On the left, the average FA value in male preterms was 0.320 ± 0.02 and in female preterms was 0.322 ± 0.01, while term children had average values of 0.353 ± 0.03 in males and 0.344 ± 0.03 in females. On the right, average FA values in preterms were 0.325 ± 0.03 in males and 0.329 ± 0.02 in females, while averages in term subjects were 0.348 ± 0.03 and 0.344 ± 0.02 in males and females respectively.

In addition to long white matter tracts, segments of subcortical white matter deep to important gyri were analyzed. Preterm children had lower FA values than term

children in white matter serving both left and right inferior precentral gyri ($p=0.0181$ and $p=0.0462$ respectively).

There was a trend towards higher FA in preterms than terms in the white matter serving the posterior portion of the left superior temporal gyrus ($p=0.0926$). The average FA values in this region were 0.194 ± 0.03 and 0.200 ± 0.03 for male and female preterm subjects respectively, and in term subjects the average values were 0.193 ± 0.02 for males and 0.182 ± 0.02 for females. There was no significant difference between the groups in the right posterior STG.

The white matter serving the inferior frontal gyrus showed significant effects of both group and gender, such that males had higher average FA values than females and the term subjects had higher FA than preterm subjects. On the left, average FA values were 0.251 ± 0.02 and 0.242 ± 0.02 in male and female preterms respectively, while term subjects had average values of 0.278 ± 0.03 in males and 0.261 ± 0.02 in females. Both group and gender differences were significant ($p<0.0001$ and $p=0.0120$ respectively). On the right, average values in preterms were 0.249 ± 0.03 and 0.247 ± 0.02 in males and females respectively, while male term subjects had average FA of 0.270 ± 0.03 and female term subjects had average FA of 0.256 ± 0.02. This difference between groups was significant ($p=0.0049$) while there was a trend for a gender effect ($p=0.0909$).

The hippocampus was analyzed in anterior, middle, and posterior divisions. On the left, there were trends for higher FA in term subjects than preterm subjects in the anterior and posterior segments, but no difference in the middle portion. On the right, anterior and middle divisions showed no significant differences, but the posterior third showed a significantly higher average FA values in terms than preterms ($p=0.0062$), with

values of 0.209 ± 0.02 and 0.211 ± 0.02 in male and female preterms respectively, while terms had average values of 0.221 ± 0.02 in males and 0.225 ± 0.02 in females.

In the forceps minor, which is the frontal radiation of the corpus callosum, there was a significant group-by-gender effect (p=0.0240) such that female preterms had greater FA values than male preterms (0.398 ± 0.02 vs. 0.382 ± 0.03 respectively) while female term subjects had lower FA values than male term subjects (0.382 ± 0.02 vs. 0.390 ± 0.02 respectively). Just inferior to this region, the right inferior frontal pole showed a significantly higher FA values in preterm subjects than terms (p=0.0398), with FA values of 0.248 ± 0.03 and 0.245 ± 0.03 in male and female subjects, compared to values of 0.237 ± 0.03 and 0.231 ± 0.02 in male and female term subjects. There were no significant differences in the left inferior frontal pole. Superior to this region, the left anterior superior frontal pole also showed higher FA values in preterm than term subjects (p=0.0188), with values of 0.224 ± 0.03 and 0.230 ± 0.02 in male and female preterm subjects, while term subjects had average values of 0.220 ± 0.02 in males and 0.210 ± 0.02 in females. There was no significant effect in the right anterior superior frontal pole.

While there were no significant differences in the anterior or posterior segments of the corona radiata, there were trends in the middle segment, such that in the left middle corona radiata, females tended to have higher FA values than males (p=0.0663), while in the right corona radiata, preterms tended to have higher FA values than terms (p=0.0594).

Table 4 **Fractional Anisotropy**

	Preterm		Term		p		
	Male	Female	Male	Female	Group	Gender	Interaction
N	26	18	17	24			
Longitudinal fasciculi							
L Arcuate	0.356 ± 0.03	0.364 ± 0.02	0.357 ± 0.03	0.354 ± 0.02	0.4047	0.5902	0.2775
R Arcuate	0.363 ± 0.03	0.368 ± 0.03	0.367 ± 0.03	0.357 ± 0.02	0.5348	0.6951	0.1660
L AIFOF	0.374 ± 0.03	0.372 ± 0.02	0.374 ± 0.02	0.369 ± 0.02	0.7656	0.4855	0.8681
R AIFOF	0.371 ± 0.04	0.380 ± 0.02	0.385 ± 0.03	0.376 ± 0.02	0.4183	0.9846	0.1667
L PIFOF	0.395 ± 0.03	0.418 ± 0.02	0.423 ± 0.02	0.421 ± 0.02	**0.0037**	0.0638	**0.0183**
R PIFOF	0.409 ± 0.03	0.420 ± 0.02	0.424 ± 0.02	0.426 ± 0.02	**0.0135**	0.1568	0.2850
L SFOF	0.290 ± 0.05	0.301 ± 0.03	0.297 ± 0.02	0.289 ± 0.03	0.7554	0.8890	0.2362
R SFOF	0.273 ± 0.05	0.289 ± 0.03	0.276 ± 0.02	0.273 ± 0.02	0.3725	0.3163	0.1876

All FA values are presented as mean value ± SD. L indicates left, and R indicates right. AIFOF indicates anterior inferior fronto-occipital fasciculus; PIFOF, posterior inferior fronto-occipital fasciculus; SFOF, superior fronto-occipital fasciculus.

Table 4 **Fractional Anisotropy**

(continued)

	Preterm		Term		p		
	Male	Female	Male	Female	Group	Gender	Interaction
Longitudinal fasciculi (continued)							
L ILF	0.305 ± 0.03	0.309 ± 0.02	0.318 ± 0.02	0.312 ± 0.02	0.1061	0.8430	0.3205
R ILF	0.302 ± 0.03	0.308 ± 0.02	0.309 ± 0.02	0.307 ± 0.02	0.4847	0.7166	0.4364
L Uncinate	0.292 ± 0.02	0.288 ± 0.02	0.311 ± 0.02	0.297 ± 0.02	**0.0042**	0.0639	0.3041
R Uncinate	0.278 ± 0.02	0.277 ± 0.01	0.298 ± 0.02	0.285 ± 0.02	**0.0020**	0.1287	0.1832
Corpus Callosum							
Genu	0.542 ± 0.05	0.553 ± 0.06	0.534 ± 0.07	0.572 ± 0.04	0.6277	**0.0377**	0.2494
Body	0.492 ± 0.04	0.497 ± 0.04	0.469 ± 0.07	0.508 ± 0.05	0.6132	0.0573	0.1226
Splenium	0.664 ± 0.05	0.672 ± 0.06	0.692 ± 0.04	0.696 ± 0.03	**0.0140**	0.5822	0.8645
Internal Capsule							
L Anterior Limb	0.397 ± 0.02	0.394 ± 0.02	0.413 ± 0.02	0.394 ± 0.02	0.0623	**0.0219**	0.0842
R Anterior Limb	0.401 ± 0.03	0.402 ± 0.02	0.411 ± 0.02	0.401 ± 0.02	0.4033	0.3535	0.2293

All FA values are presented as mean value ± SD. L indicates left, and R indicates right. ILF indicates inferior longitudinal fasciculus.

Table 4 **Fractional Anisotropy**

(continued)

	Preterm		Term		p		
	Male	Female	Male	Female	Group	Gender	Interaction
Internal Capsule (continued)							
L Posterior Limb	0.500 ± 0.03	0.504 ± 0.02	0.515 ± 0.02	0.503 ± 0.02	0.1680	0.4664	0.1099
R Posterior Limb	0.492 ± 0.02	0.502 ± 0.02	0.504 ± 0.02	0.502 ± 0.01	0.1456	0.3274	0.1468
External Capsule							
L External Capsule	0.320 ± 0.02	0.322 ± 0.01	0.353 ± 0.03	0.344 ± 0.03	**<0.0001**	0.5144	0.2837
R External Capsule	0.325 ± 0.03	0.329 ± 0.02	0.348 ± 0.03	0.344 ± 0.02	**0.0007**	0.9413	0.4805
Subcortical White Matter Regions							
L Inferior PCG	0.252 ± 0.03	0.258 ± 0.03	0.270 ± 0.03	0.268 ± 0.02	**0.0181**	0.7197	0.5131
R Inferior PCG	0.256 ± 0.02	0.260 ± 0.02	0.266 ± 0.02	0.268 ± 0.02	**0.0462**	0.5598	0.8271
L Posterior STG	0.194 ± 0.03	0.200 ± 0.03	0.193 ± 0.02	0.182 ± 0.02	0.0926	0.7589	0.1284
R Posterior STG	0.200 ± 0.02	0.203 ± 0.02	0.205 ± 0.02	0.200 ± 0.02	0.8766	0.8649	0.3829

All FA values are presented as mean value ± SD. L indicates left, and R indicates right. PCG indicates precentral gyrus; STG, superior temporal gyrus.

Table 4 **Fractional Anisotropy**

(continued)

	Preterm		Term		p		
	Male	Female	Male	Female	Group	Gender	Interaction
L IFG	0.251 ± 0.02	0.242 ± 0.02	0.278 ± 0.03	0.261 ± 0.02	**<0.0001**	**0.0123**	0.4420
R IFG	0.249 ± 0.03	0.247 ± 0.02	0.270 ± 0.03	0.256 ± 0.02	**0.0049**	0.0909	0.2556
L DLPFWM	0.226 ± 0.02	0.223 ± 0.02	0.231 ± 0.02	0.225 ± 0.02	0.4338	0.3226	0.7721
R DLPFWM	0.225 ± 0.02	0.220 ± 0.01	0.241 ± 0.03	0.229 ± 0.03	**0.0092**	0.0635	0.4093
Limbic system tracts							
L Anterior Hipp.	0.157 ± 0.02	0.154 ± 0.02	0.166 ± 0.02	0.161 ± 0.02	0.0723	0.3936	0.8311
R Anterior Hipp.	0.171 ± 0.02	0.162 ± 0.02	0.170 ± 0.03	0.165 ± 0.01	0.8593	0.1318	0.7354
L Middle Hipp.	0.205 ± 0.02	0.207 ± 0.02	0.215 ± 0.02	0.206 ± 0.02	0.2958	0.4354	0.1676
R Middle Hipp.	0.209 ± 0.02	0.211 ± 0.02	0.221 ± 0.02	0.212 ± 0.02	0.1501	0.3743	0.2269
L Posterior Hipp.	0.197 ± 0.02	0.197 ± 0.02	0.210 ± 0.02	0.205 ± 0.03	0.0541	0.6087	0.5980
R Posterior Hipp.	0.209 ± 0.02	0.211 ± 0.02	0.221 ± 0.02	0.225 ± 0.02	**0.0062**	0.4875	0.7295

All FA values are presented as mean value ± SD. L indicates left, and R indicates right. IFG indicates inferior frontal gyrus; DLPFWM, dorsolateral prefrontal white matter; Hipp., hippocampus.

Table 4 **Fractional Anisotropy**

(continued)

	Preterm		Term		p		
	Male	Female	Male	Female	Group	Gender	Interaction
Limbic system tracts (continued)							
L Cingulum	0.309 ± 0.06	0.313 ± 0.03	0.317 ± 0.04	0.326 ± 0.03	0.2237	0.4697	0.8065
R Cingulum	0.297 ± 0.05	0.311 ± 0.04	0.310 ± 0.03	0.321 ± 0.03	0.1663	0.1349	0.8217
L Fornix	0.377 ± 0.04	0.381 ± 0.03	0.386 ± 0.03	0.386 ± 0.04	0.3478	0.8075	0.8351
R Fornix	0.374 ± 0.04	0.372 ± 0.03	0.372 ± 0.03	0.386 ± 0.04	0.4102	0.4217	0.2963
Other Regions							
L Forceps Major	0.330 ± 0.05	0.356 ± 0.04	0.356 ± 0.05	0.357 ± 0.03	0.1489	0.1478	0.1722
R Forceps Major	0.350 ± 0.04	0.365 ± 0.03	0.370 ± 0.04	0.368 ± 0.02	0.1425	0.3867	0.2896
L Forceps Minor	0.374 ± 0.03	0.381 ± 0.02	0.382 ± 0.02	0.374 ± 0.02	0.9450	0.9284	0.1541
R Forceps Minor	0.382 ± 0.03	0.398 ± 0.02	0.390 ± 0.02	0.382 ± 0.02	0.4031	0.4126	**0.0242**

All FA values are presented as mean value ± SD. L indicates left, and R indicates right.

Table 4 **Fractional Anisotropy**

(continued)

	Preterm		Term		p		
	Male	Female	Male	Female	Group	Gender	Interaction
Other Regions (continued)							
L Anterior CorRadiata	0.352 ± 0.03	0.350 ± 0.02	0.354 ± 0.02	0.351 ± 0.02	0.6895	0.5975	0.9872
R Anterior CorRadiata	0.352 ± 0.02	0.358 ± 0.02	0.354 ± 0.02	0.353 ± 0.02	0.7028	0.6622	0.4028
L Middle CorRadiata	0.385 ± 0.02	0.395 ± 0.02	0.383 ± 0.02	0.387 ± 0.01	0.2091	0.0663	0.4609
R Middle CorRadiata	0.386 ± 0.02	0.397 ± 0.02	0.383 ± 0.02	0.385 ± 0.02	0.0594	0.1121	0.2543
L Posterior CorRadiata	0.323 ± 0.03	0.327 ± 0.01	0.324 ± 0.03	0.323 ± 0.02	0.7969	0.8675	0.6194
R Posterior CorRadiata	0.318 ± 0.03	0.318 ± 0.02	0.319 ± 0.02	0.318 ± 0.02	0.9000	0.9929	0.9359
L Inf. Frontal Pole	0.251 ± 0.03	0.243 ± 0.03	0.243 ± 0.03	0.238 ± 0.02	0.3165	0.2872	0.8033
R Inf. Frontal Pole	0.248 ± 0.03	0.245 ± 0.03	0.237 ± 0.03	0.231 ± 0.02	**0.0398**	0.4201	0.7867
L Ant. Sup. Frontal Pole	0.224 ± 0.03	0.230 ± 0.02	0.220 ± 0.02	0.210 ± 0.02	**0.0188**	0.7302	0.1206
R Ant. Sup. Frontal Pole	0.217 ± 0.03	0.209 ± 0.03	0.207 ± 0.02	0.203 ± 0.02	0.1561	0.3083	0.8101

All FA values are presented as mean value ± SD. L indicates left, and R indicates right. CorRadiata indicates corona radiata; Inf., inferior; Ant. Sup., anterior superior

Table 5. Correlations between FA in specific ROIs and cognitive testing

Correlations between FA in specific ROIs and selected cognitive tests are presented in Table 5. Scores on PPVT, a measure of semantic processing, are correlated with left and right uncinate fasciculi, left and right external capsules, and white matter serving the left and right inferior frontal gyri. Rapid Naming Composite scores, a subset of CTOPP testing highlighting phonological processing, are correlated with left and right arcuate fasciculi.

In Table 5A, these correlations are presented for all subjects (n=85), with statistical modeling taking into account age at scan, preterm vs. term status, and gender. In this analysis, there are significant positive correlations between PPVT scores and bilateral uncinate fasciculi: on the left, R^2=0.1109, with p=0.0107, and on the right, R^2=0.1138 with p=0.0092. Trends also exist for positive correlations between Rapid Naming Composite scores and bilateral arcuate fasciculi: on the left, R^2=0.1077, with p=0.0774, while on the right, R^2=0.1116, with p=0.0625. There are no significant associations between PPVT scores and left and right external capsules or white matter deep to the IFG.

In Table 5B, the data from the preterm group alone is analyzed with statistical consideration of birthweight and the presence of bronchopulmonary dysplasia in addition to age at scan and gender. With this consideration, there remains a significant positive association between FA values in the right uncinate fasciculus and PPVT scores in the preterm group (R^2=0.1712, p=0.0273) and a similar positive trend between these scores and values in the left uncinate (R^2=0.1401, p=0.0605). The positive correlation between PPVT scores and the right uncinate fasciculus is now a trend (R^2=0.1269, p=0.0848). FA

values in both left and right arcuate fasciculi again show significant positive correlations with CTOPP Rapid Naming Composite scores in the preterm group. On the left, correlations with Rapid Naming scores show R^2=0.3374 and p=0.0051, while the right arcuate correlates with these scores such that R^2=0.2796 and p=0.0284.

Because previous studies in this cohort at age 12 demonstrated gender effects, we tested the effect of gender in the models for the correlations between uncinate and arcuate to language testing. FA in the right uncinate contributed to PPVT for the preterm males (R^2=0.2559, p=0.0186), while FA in the left and right arcuate each contributed to CTOPP Rapid Naming scores in the preterm females (left: R^2=0.5582, p=0.0167; right: R^2=0.5364, p=0.0229).

Finally, there were no significant correlations in the term population.

Table 5A Correlations
All subjects
Corrected for Age at scan, Group, Gender

Test	Region	R^2	p
PPVT	L uncinate	**0.1109**	**0.0107**
	R uncinate	**0.1138**	**0.0092**
	L external capsule	0.0399	0.4825
	R external capsule	0.0611	0.1343
	L IFG	0.0352	0.7425
	R IFG	0.0353	0.7359
CTOPP Rapid Naming Composite	L arcuate	0.1077	0.0774
	R arcuate	0.1116	0.0625

Table 5B Correlations
Preterm subjects
Corrected for Age at scan, Gender, BW, BPD

Test	Region	R^2	p
PPVT	L uncinate	0.1401	0.0605
	R uncinate	**0.1712**	**0.0273**
	L external capsule	0.0825	0.26
	R external capsule	0.1269	0.0848
	L IFG	0.0686	0.4354
	R IFG	0.0626	0.5407
CTOPP Rapid Naming Composite	L arcuate	**0.3374**	**0.0051**
	R arcuate	**0.2796**	**0.0284**

PPVT: Peabody Picture Vocabulary - Revised; CTOPP: Comprehensive Test of Phonological Processing; L: left; R: right; IFG: inferior frontal gyrus; BW: birthweight; BPD: bronchopulmonary dysplasia

Figure 2. Correlations between FA in specific ROIs and cognitive testing

Graphic representations of significant correlations between FA values in select ROIs and scores on specific cognitive tests are presented in Figure 2, with dots representing each subject, a solid line representing the R value for the regression model, and dotted lines representing a 95% confidence interval for the correlation. Each graph represents data seen in Table 5.

In Figure 2A, correlations between PPVT scores and FA of the left uncinate for all subjects (n=85) are presented. Figure 2B shows the correlations between all subjects' PPVT scores and right uncinate FA. Figure 2C focuses on preterm subjects' correlation between PPVT scores and FA in the left uncinate. In Figure 2D, PPVT scores of preterm subjects are correlated with the FA values in the right uncinate fasciculus. Figure 2E shows the Rapid Naming Composite scores of all subjects correlating with FA in the left arcuate. In Figure 2F, all subjects' Rapid Naming Composite scores correlate with FA in the right arcuate. Figure 2G shows the Rapid Naming Composite scores of preterm subjects correlating with FA of the left arcuate. Finally, Figure 2H demonstrates preterm subjects' Rapid Naming Composite scores correlating with FA of the right arcuate.

Figure 2

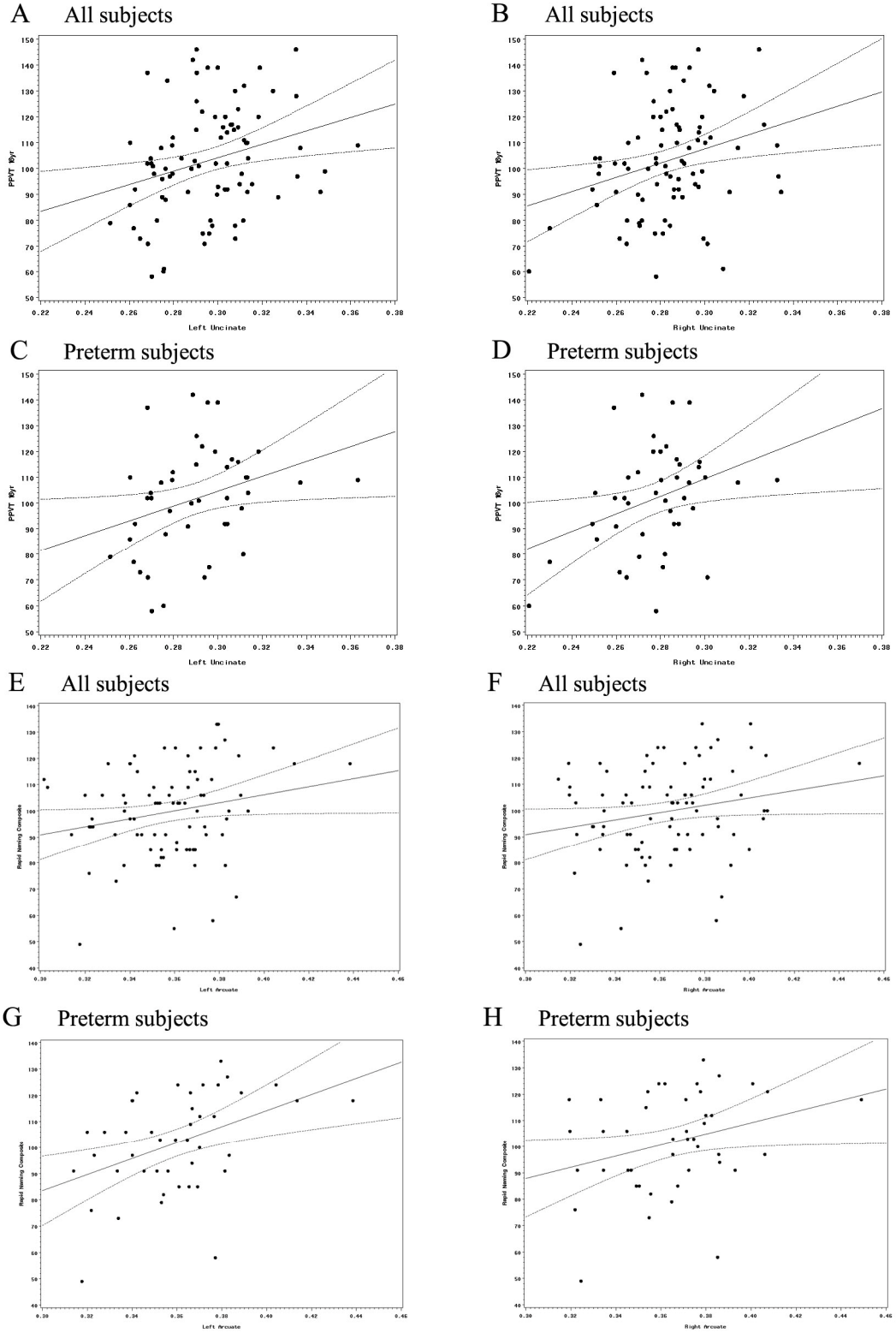

Figure 2. Graphs show the relationship between testing scores on the y axis (PPVT in A – D; CTOPP Rapid Naming Composite scores in E – H) and FA values in specific regions on the x axis (left uncinate in A, C; right uncinate in B, D; left arcuate in E, G; right arcuate in F, H). The dashed lines represent 95% confidence intervals. Each black dot represents data from a single subject.

Discussion

Neonatal data

The group of infants participating in this study did not show evidence of severe brain injury as infants, but one quarter did develop bronchopulmonary dysplasia. Chronic lung disease has been shown to have an effect on FA measures in the brain independent of variables in preterm subject such as gestational age (52). The presence of BPD, along with birthweight, was taken into account in statistical modeling of the correlation between cognitive scoring and FA values in Tables 5c and 5d. Birthweight, which also has been shown to impact FA measures (45), was also taken into account in Tables 5c and 5d.

Demographic data

While males outnumbered females in the preterm group, there were more females than males in the control term group. Given previously reported differences in outcomes between male and female preterm subjects (14), gender was taken into account in statistical models for comparison of cognitive data, fractional anisotropy values, and correlations between the two, and average scores and values are presented separately for males and females in each table.

Potential factors which could influence cognitive performance or brain structure include levels of maternal education, which is likely to affect performance on cognitive exams, and percentage of right-handed subjects, which impacts laterality of language within the brain. There were higher numbers of left-handed subjects and a trend for lower

levels of maternal education in the preterm cohort than in the term group, though neither was significant.

Cognitive data

Preterm subjects showed impairment relative to term control subjects on multiple tests, including WISC full scale IQ, verbal IQ, and performance IQ, VMI, and the CTOPP Phonological Awareness Composite score, with particular difficulties with Segmented Non-Words. Notably, while preterm subjects had lower average scores on multiple IQ measures than term controls, their scores were comparable to term subjects on certain tests. Specifically, preterms performed well on PPVT, TOWRE, CTOPP Rapid Naming Composite scores, Non-Word Repetition, and Phoneme Reversal. Good performance on CTOPP components including repetition may indicate preserved phonological processing ability, PPVT measures semantic understanding through testing of receptive vocabulary, and TOWRE is a measure of reading ability. These preserved abilities span a range of different subsystems of linguistic processing and ability.

Fractional anisotropy

Our data show lower FA values, implying white matter microstructural disorganization, in multiple white matter areas in preterm subjects without evidence of severe neonatal brain injury. These alterations in white matter were seen in long intrahemispheric association tracts, interhemispheric connections, limbic structures, and frontal lobe white matter areas. The splenium, which has multiple cross-hemispheric connections and is the last part of the corpus callosum to develop, shows particular

deficits in FA in preterm subjects compared to term subjects; this is consistent with reports from multiple cohorts (30, 87-89). Deficits in FA in the white matter of the hippocampus may indicate barriers to working memory, and is consistent with evidence from an animal model showing anisotropy decreases in hippocampi along with difficulties in spatial memory (90). Previous reports in children have also suggested that preterm birth impacts the hippocampi, showing volume losses in the hippocampi of preterm children compared to controls (91). The posterior segment of the inferior fronto-occipital fasciculus, a bundle of intrahemispheric connection fibers, again shows bilateral deficits in FA in preterm subjects relative to term subjects, consistent with the finding at 12 years of age (30).

There are significant differences between terms and preterms in the areas implicated in the ventral pathway of language processing. Bilateral uncinate fasciculi show decreased FA in preterm subjects. In addition, bilateral external capsules, areas which include fibers in the extreme capsule (since the resolution of the study did not permit separation of the two tracts), show decreased FA in preterms. The white matter serving the IFG, which is contiguous with the uncinate fasciculus, also shows bilateral deficits in FA in the preterm group. Of note, the arcuate fasciculus, the primary component of the dorsal, phonological language processing pathway, shows no significant FA differences between terms and preterms.

While previous reports have noted FA deficits in the posterior limb of the internal capsule in preterm subjects, no such deficit was noted in our cohort. These previous studies included higher percentage of subjects with severe brain injury at birth leading to cerebral palsy and severe neurological deficits. White matter deep to the inferior portion

of the precentral gyrus, however, does show decreased FA in preterms bilaterally in our study; deficits in this region, which supplies motor fibers to the hands and face, may imply alterations in gyration or subtle rearrangement of motor pathways at a subcortical level.

Several regions, in contrast, showed higher average FA values in preterms then term subjects. These regions included white matter of the right inferior frontal pole, and white matter of the left anterior superior frontal pole. The significance of these differences is uncertain; it is possible that preterms have developed different patterns of gyration in the deep white matter of the frontal lobe which map differently onto our ROIs. This could represent an alternate pattern of frontal white matter development in preterm children.

Correlations

In preterm subjects, better scores on language tests were associated with higher FA values in regions associated with language processing. Language scores which showed correlations with FA represented tests which preterm subjects performed, on average, as well as term controls. These score subsets, in other words, were those in which preterm subjects had been successful in compensating for the injury of preterm birth.

The strength of anatomical connectivity in a dorsal pathway, the arcuate fasciculus, is correlated bilaterally with performance on a phonologic task (CTOPP Rapid Naming Composite score), as shown in Table 5. This correlation between a phonological task and bilateral dorsal pathways, in place of the typical left-sided dominance (74), may

imply that preterm subjects rely more heavily on the right hemisphere for performance of language tasks than in normally developing subjects. This effect was strongest in preterm females, who also had the highest average Rapid Naming Composite score, implying successful compensation for the injury of prematurity on this task. Of note, preterm females have previously been reported to have better immediate and longterm outcomes than males born at equivalent gestational age (14, 15).

Connectivity in a ventral pathway (the uncinate fasciculus) correlated bilaterally with performance on a semantic language task (PPVT). Within the preterm group, right-sided correlations were stronger than left-sided correlations, again highlighting the importance of right hemispheric pathways for language function in this cohort.

Term subjects did not show correlations between language scores and FA values in the tested regions. Since their FA values and testing scores were within the normal range, the variability within these parameters may not have permitted adequate power for these analyses.

Limitations and future directions

Limitations of our study include the sample size and the lack of advanced imaging in the neonatal period; though our cohort lacked severe brain injury such as intraventricular hemorrhage, subtle white matter injury undetectable by cranial ultrasonography is not excluded and may have influenced the outcomes of these children. 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. While the correlation of FA in selected regions and scores on language subsets indicates a relationship between white matter microstructure and test performance, this does not give information about causation. 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.

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, white matter tracts, and gender are 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 develop uniform terminology in reference to brain regions. This will avoid the possible subjectivity of manual segmentation of ROIs and 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.

Conclusion

These data, overall, present a complex picture of cognitive deficits and microstructural change in the brains of preterm adolescents. Sixteen years after the insult of preterm birth, preterm subjects continue to show impaired performance on multiple

aspects of neuropsychological testing including verbal, performance, and visuomotor subsets. Imaging of these subjects also shows microstructural abnormalities in multiple white matter tracts including interhemispheric and intrahemispheric association fibers.

Further, our data provide the first evidence that dual processing systems underlie language function in adolescents born preterm. The dual language system has been proposed to include a left-sided dorsal pathway associated with phonological and articulatory processing (arcuate fasciculus), and a bilateral ventral pathway for semantic, receptive language processing (uncinate fasciculus). Moreover, the marked correlations found in our preterm population between phonological test performance and FA of the dorsal pathway are bilateral. This represents a departure from the left-sided lateralization of the dorsal articulatory pathway in typically developing subjects, and suggests increased utilization of the right hemisphere in preterm subjects compared to those born at term. This may represent either a delay in maturation or the engagement of alternative neural pathways for language in the developing preterm brain.

References

1. Martin JA, Kung HC, Mathews TJ, et al. Annual summary of vital statistics: 2006. Pediatrics 2008;121(4):788-801.

2. Dyet LE, Kennea N, Counsell SJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. Pediatrics 2006;118(2):536-48.

3. Miller SP, Ferriero DM, Leonard C, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. J Pediatr 2005;147(5):609-16.

4. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. N Engl J Med 2002;346(3):149-57.

5. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196(2):147 e1-8.

6. Hack M. Adult outcomes of preterm children. J Dev Behav Pediatr 2009;30(5):460-70.

7. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8(1):110-24.

8. McClure MM, Riddle A, Manese M, et al. Cerebral blood flow heterogeneity in preterm sheep: lack of physiologic support for vascular boundary zones in fetal cerebral white matter. J Cereb Blood Flow Metab 2008;28(5):995-1008.

9. Riddle A, Luo NL, Manese M, et al. Spatial heterogeneity in oligodendrocyte lineage maturation and not cerebral blood flow predicts fetal ovine periventricular white matter injury. J Neurosci 2006;26(11):3045-55.

10. Haynes RL, Billiards SS, Borenstein NS, Volpe JJ, Kinney HC. Diffuse axonal injury in periventricular leukomalacia as determined by apoptotic marker fractin. Pediatr Res 2008;63(6):656-61.

11. Scafidi J, Fagel DM, Ment LR, Vaccarino FM. Modeling premature brain injury and recovery. Int J Dev Neurosci 2009;27(8):863-71.

12. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. Eur J Pediatr 2008;167(1):87-95.

13. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. Pediatrics 2009;123(3):1037-44.

14. Reiss AL, Kesler SR, Vohr B, et al. Sex differences in cerebral volumes of 8-year-olds born preterm. J Pediatr 2004;145(2):242-9.

15. Kesler SR, Reiss AL, Vohr B, et al. Brain volume reductions within multiple cognitive systems in male preterm children at age twelve. J Pediatr 2008;152(4):513-20, 20 e1.

16. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352(1):9-19.

17. Kraemer S. The fragile male. Bmj 2000;321(7276):1609-12.

18. Als H, Duffy FH, McAnulty GB, et al. Early experience alters brain function and structure. Pediatrics 2004;113(4):846-57.

19. Ment LR, Vohr B, Allan W, et al. Change in cognitive function over time in very low-birth-weight infants. Jama 2003;289(6):705-11.

20. Schafer RJ, Lacadie C, Vohr B, et al. Alterations in functional connectivity for language in prematurely born adolescents. Brain 2009;132(Pt 3):661-70.

21. Ment LR, Peterson BS, Vohr B, et al. Cortical recruitment patterns in children born prematurely compared with control subjects during a passive listening functional magnetic resonance imaging task. J Pediatr 2006;149(4):490-8.

22. Ment LR, Constable RT. Injury and recovery in the developing brain: evidence from functional MRI studies of prematurely born children. Nat Clin Pract Neurol 2007;3(10):558-71.

23. Counsell SJ, Boardman JP. Differential brain growth in the infant born preterm: current knowledge and future developments from brain imaging. Semin Fetal Neonatal Med 2005;10(5):403-10.

24. Ment LR, Hirtz D, Huppi PS. Imaging biomarkers of outcome in the developing preterm brain. Lancet Neurol 2009;8(11):1042-55.

25. Myers E, Ment LR. Long-term outcome of preterm infants and the role of neuroimaging. Clin Perinatol 2009;36(4):773-89, vi.

26. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355(7):685-94.

27. Maalouf EF, Duggan PJ, Rutherford MA, et al. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. J Pediatr 1999;135(3):351-7.

28. Kesler SR, Ment LR, Vohr B, et al. Volumetric analysis of regional cerebral development in preterm children. Pediatr Neurol 2004;31(5):318-25.

29. Gimenez M, Junque C, Narberhaus A, Bargallo N, Botet F, Mercader JM. White matter volume and concentration reductions in adolescents with history of very preterm birth: a voxel-based morphometry study. Neuroimage 2006;32(4):1485-98.

30. Constable RT, Ment LR, Vohr BR, et al. Prematurely born children demonstrate white matter microstructural differences at 12 years of age, relative to term control subjects: an investigation of group and gender effects. Pediatrics 2008;121(2):306-16.

31. Ment LR, Kesler S, Vohr B, et al. Longitudinal brain volume changes in preterm and term control subjects during late childhood and adolescence. Pediatrics 2009;123(2):503-11.

32. Jackowski M, Kao CY, Qiu M, Constable RT, Staib LH. White matter tractography by anisotropic wavefront evolution and diffusion tensor imaging. Med Image Anal 2005;9(5):427-40.

33. Jones DK, Simmons A, Williams SC, Horsfield MA. Non-invasive assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. Magn Reson Med 1999;42(1):37-41.

34. Hasan KM, Halphen C, Sankar A, et al. Diffusion tensor imaging-based tissue segmentation: validation and application to the developing child and adolescent brain. Neuroimage 2007;34(4):1497-505.

35. Huppi PS, Dubois J. Diffusion tensor imaging of brain development. Semin Fetal Neonatal Med 2006;11(6):489-97.

36. Lee SK, Kim DI, Kim J, et al. Diffusion-tensor MR imaging and fiber tractography: a new method of describing aberrant fiber connections in developmental CNS anomalies. Radiographics 2005;25(1):53-65; discussion 6-8.

37. Mukherjee P, McKinstry RC. Diffusion tensor imaging and tractography of human brain development. Neuroimaging Clin N Am 2006;16(1):19-43, vii.

38. Neil J, Miller J, Mukherjee P, Huppi PS. Diffusion tensor imaging of normal and injured developing human brain - a technical review. NMR Biomed 2002;15(7-8):543-52.

39. Assaf Y, Blumenfeld-Katzir T, Yovel Y, Basser PJ. AxCaliber: a method for measuring axon diameter distribution from diffusion MRI. Magn Reson Med 2008;59(6):1347-54.

40. Dudink J, Kerr JL, Paterson K, Counsell SJ. Connecting the developing preterm brain. Early Hum Dev 2008;84(12):777-82.

41. Huppi PS, Maier SE, Peled S, et al. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. Pediatr Res 1998;44(4):584-90.

42. Huppi PS, Murphy B, Maier SE, et al. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. Pediatrics 2001;107(3):455-60.

43. Bui T, Daire JL, Chalard F, et al. Microstructural development of human brain assessed in utero by diffusion tensor imaging. Pediatr Radiol 2006;36(11):1133-40.

44. Anjari M, Counsell SJ, Srinivasan L, et al. The association of lung disease with cerebral white matter abnormalities in preterm infants. Pediatrics 2009;124(1):268-76.

45. Andrews JS, Ben-Shachar M, Yeatman JD, Flom LL, Luna B, Feldman HM. Reading performance correlates with white-matter properties in preterm and term children. Dev Med Child Neurol 2009.

46. Aeby A, Liu Y, De Tiege X, et al. Maturation of thalamic radiations between 34 and 41 weeks' gestation: a combined voxel-based study and probabilistic tractography with diffusion tensor imaging. AJNR Am J Neuroradiol 2009;30(9):1780-6.

47. Gimenez M, Miranda MJ, Born AP, Nagy Z, Rostrup E, Jernigan TL. Accelerated cerebral white matter development in preterm infants: a voxel-based morphometry study with diffusion tensor MR imaging. Neuroimage 2008;41(3):728-34.

48. Chau V, Poskitt KJ, McFadden DE, et al. Effect of chorioamnionitis on brain development and injury in premature newborns. Ann Neurol 2009;66(2):155-64.

49. Miller SP, Vigneron DB, Henry RG, et al. Serial quantitative diffusion tensor MRI of the premature brain: development in newborns with and without injury. J Magn Reson Imaging 2002;16(6):621-32.

50. Partridge SC, Mukherjee P, Henry RG, et al. Diffusion tensor imaging: serial quantitation of white matter tract maturity in premature newborns. Neuroimage 2004;22(3):1302-14.

51. Berman JI, Mukherjee P, Partridge SC, et al. Quantitative diffusion tensor MRI fiber tractography of sensorimotor white matter development in premature infants. Neuroimage 2005;27(4):862-71.

52. Anjari M, Srinivasan L, Allsop JM, et al. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. Neuroimage 2007;35(3):1021-7.

53. Dudink J, Lequin M, van Pul C, et al. Fractional anisotropy in white matter tracts of very-low-birth-weight infants. Pediatr Radiol 2007;37(12):1216-23.

54. Rose SE, Hatzigeorgiou X, Strudwick MW, Durbridge G, Davies PS, Colditz PB. Altered white matter diffusion anisotropy in normal and preterm infants at term-equivalent age. Magn Reson Med 2008;60(4):761-7.

55. Cheong JL, Thompson DK, Wang HX, et al. Abnormal white matter signal on MR imaging is related to abnormal tissue microstructure. AJNR Am J Neuroradiol 2009;30(3):623-8.

56. Counsell SJ, Dyet LE, Larkman DJ, et al. Thalamo-cortical connectivity in children born preterm mapped using probabilistic magnetic resonance tractography. Neuroimage 2007;34(3):896-904.

57. Vangberg TR, Skranes J, Dale AM, Martinussen M, Brubakk AM, Haraldseth O. Changes in white matter diffusion anisotropy in adolescents born prematurely. Neuroimage 2006;32(4):1538-48.

58. Nagy Z, Westerberg H, Skare S, et al. Preterm children have disturbances of white matter at 11 years of age as shown by diffusion tensor imaging. Pediatr Res 2003;54(5):672-9.

59. Yung A, Poon G, Qiu DQ, et al. White matter volume and anisotropy in preterm children: a pilot study of neurocognitive correlates. Pediatr Res 2007;61(6):732-6.

60. Skranes J, Vangberg TR, Kulseng S, et al. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain 2007;130(Pt 3):654-66.

61. Counsell SJ, Edwards AD, Chew AT, et al. Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm. Brain 2008;131(Pt 12):3201-8.

62. Murakami A, Morimoto M, Yamada K, et al. Fiber-tracking techniques can predict the degree of neurologic impairment for periventricular leukomalacia. Pediatrics 2008;122(3):500-6.

63. Kontis D, Catani M, Cuddy M, et al. Diffusion tensor MRI of the corpus callosum and cognitive function in adults born preterm. Neuroreport 2009;20(4):424-8.

64. Nagy Z, Ashburner J, Andersson J, et al. Structural correlates of preterm birth in the adolescent brain. Pediatrics 2009;124(5):e964-72.

65. Drobyshevsky A, Bregman J, Storey P, et al. Serial diffusion tensor imaging detects white matter changes that correlate with motor outcome in premature infants. Dev Neurosci 2007;29(4-5):289-301.

66. Peterson BS, Vohr B, Staib LH, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. Jama 2000;284(15):1939-47.

67. Arzoumanian Y, Mirmiran M, Barnes PD, et al. Diffusion tensor brain imaging findings at term-equivalent age may predict neurologic abnormalities in low birth weight preterm infants. AJNR Am J Neuroradiol 2003;24(8):1646-53.

68. Krishnan ML, Dyet LE, Boardman JP, et al. Relationship between white matter apparent diffusion coefficients in preterm infants at term-equivalent age and developmental outcome at 2 years. Pediatrics 2007;120(3):e604-9.

69. Rose J, Mirmiran M, Butler EE, et al. Neonatal microstructural development of the internal capsule on diffusion tensor imaging correlates with severity of gait and motor deficits. Dev Med Child Neurol 2007;49(10):745-50.

70. Rose J, Butler EE, Lamont LE, Barnes PD, Atlas SW, Stevenson DK. Neonatal brain structure on MRI and diffusion tensor imaging, sex, and neurodevelopment in very-low-birthweight preterm children. Dev Med Child Neurol 2009;51(7):526-35.

71. Bassi L, Ricci D, Volzone A, et al. Probabilistic diffusion tractography of the optic radiations and visual function in preterm infants at term equivalent age. Brain 2008;131(Pt 2):573-82.

72. Berman JI, Glass HC, Miller SP, et al. Quantitative fiber tracking analysis of the optic radiation correlated with visual performance in premature newborns. AJNR Am J Neuroradiol 2009;30(1):120-4.

73. Hoon AH, Jr., Stashinko EE, Nagae LM, et al. Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways. Dev Med Child Neurol 2009;51(9):697-704.

74. Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci 2007;8(5):393-402.

75. Friederici AD. Pathways to language: fiber tracts in the human brain. Trends Cogn Sci 2009;13(4):175-81.

76. Saur D, Kreher BW, Schnell S, et al. Ventral and dorsal pathways for language. Proc Natl Acad Sci U S A 2008;105(46):18035-40.

77. Parker GJ, Luzzi S, Alexander DC, Wheeler-Kingshott CA, Ciccarelli O, Lambon Ralph MA. Lateralization of ventral and dorsal auditory-language pathways in the human brain. Neuroimage 2005;24(3):656-66.

78. Gozzo Y, Vohr B, Lacadie C, et al. Alterations in neural connectivity in preterm children at school age. Neuroimage 2009;48(2):458-63.

79. Brauer J, Friederici AD. Functional neural networks of semantic and syntactic processes in the developing brain. J Cogn Neurosci 2007;19(10):1609-23.

80. Peterson BS, Vohr B, Kane MJ, et al. A functional magnetic resonance imaging study of language processing and its cognitive correlates in prematurely born children. Pediatrics 2002;110(6):1153-62.

81. Chou TL, Booth JR, Burman DD, et al. Developmental changes in the neural correlates of semantic processing. Neuroimage 2006;29(4):1141-9.

82. Cao F, Peng D, Liu L, et al. Developmental differences of neurocognitive networks for phonological and semantic processing in Chinese word reading. Hum Brain Mapp 2009;30(3):797-809.

83. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics 1994;93(4):543-50.

84. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. J Pediatr 1994;124(6):951-5.

85. Vohr BR, Allan WC, Westerveld M, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics 2003;111(4 Pt 1):e340-6.

86. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. Radiology 2004;230(1):77-87.

87. Caldu X, Narberhaus A, Junque C, et al. Corpus callosum size and neuropsychologic impairment in adolescents who were born preterm. J Child Neurol 2006;21(5):406-10.

88. Anderson NG, Laurent I, Woodward LJ, Inder TE. Detection of impaired growth of the corpus callosum in premature infants. Pediatrics 2006;118(3):951-60.

89. Narberhaus A, Segarra D, Caldu X, et al. Gestational age at preterm birth in relation to corpus callosum and general cognitive outcome in adolescents. J Child Neurol 2007;22(6):761-5.

90. Chahboune H, Ment LR, Stewart WB, et al. Hypoxic injury during neonatal development in murine brain: correlation between in vivo DTI findings and behavioral assessment. Cereb Cortex 2009;19(12):2891-901.

91. Isaacs EB, Edmonds CJ, Chong WK, Lucas A, Morley R, Gadian DG. Brain morphometry and IQ measurements in preterm children. Brain 2004;127(Pt 12):2595-607.